Official Protocol Title:	A Phase 2, Open-label Study to Evaluate the Safety and Efficacy of MK-7684A (MK-7684 [Vibostolimab] with MK-3475 [Pembrolizumab] Coformulation) in Participants with Relapsed or Refractory Hematological Malignancies
NCT number:	NCT05005442
Document Date:	19-Dec-2023

TITLE PAGE

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Protocol Title: A Phase 2, Open-label Study to Evaluate the Safety and Efficacy of MK-7684A (MK-7684 [Vibostolimab] with MK-3475 [Pembrolizumab] Coformulation) in Participants with Relapsed or Refractory Hematological Malignancies

Protocol Number: 004-05

Compound Number: MK-7684A

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	154973
EU CT	Not applicable
EudraCT	2021-001700-15
JRCT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	154973

Approval Date: 19 December 2023

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2, Open-label Study to Evaluate the Safety and Efficacy of MK-7684A (MK-7684 [Vibostolimab] with MK-3475 [Pembrolizumab] Coformulation) in Participants with Relapsed or Refractory Hematological Malignancies

Short Title: A Phase 2 Study of MK-7684A in Relapsed/Refractory Hematological Malignancies

Acronym: MK-7684A-004

Hypotheses, Objectives, and Endpoints:

Formal hypothesis testing will not be performed in this protocol. In male and female participants who are 18 years of age or older with various relapsed/refractory hematological malignancies.

Tertiary/exploratory endpoints will not be collected after the end of the study.

Primary Objective	**Primary Endpoint**
Part 1: To determine the safety and tolerability of MK-7684A (Cohorts A to F)	Dose-Limiting Toxicities Adverse events Discontinuation of study intervention due to an AE.
Secondary Objectives	**Secondary Endpoints**
Part 1: To evaluate ORR following administration of MK-7684A (Cohorts A to F) per disease-specific criteria as assessed by the investigator.	Objective response: CR or PR (for MM includes stringent CR, CR, and VGPR, PR)
Part 1: To evaluate the DOR following administration of MK-7684A (Cohorts A to F)	DOR, defined as the time from first documented evidence of CR or PR (for MM includes stringent CR, CR, and VGPR, PR) until disease progression per disease-specific criteria as assessed by the investigator or death due to any cause, whichever occurs first.

Part 1: To evaluate the DCR following administration of MK-7684A (Cohorts A to F)	DCR: CR, PR or SD (for MM, also including stringent CR, VGPR, MR) for at least 12 weeks prior to any evidence of progression.
Part 1: To characterize the PK profile of vibostolimab (Cohorts A to F)	Trough concentration (C_{trough}) Maximum concentration (C_{max})

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Haematological malignancy
Population	Participants with cHL or PMBCL, FL, DLBCL, MM, and NHL
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 180 participants with various hematological malignancies will be treated in the signal finding (Part 1) and approximately 150 participants may be treated in cohort expansion (Part 2), if initiated. Part 1 will involve 6 cohorts (Cohorts A to F relapsed/refractory: cHL or PMBCL not previously treated with an anti-PD-1/L1 agent, cHL or PMBCL previously treated with an anti-PD-1/L1 agent, FL, DLBCL, MM, and NHL) of approximately 30 participants per cohort treated with MK-7684A, a coformulation of vibostolimab and pembrolizumab. Part 2 may involve the expansion of Cohorts B to E (cHL or PMBCL previously treated with an anti-PD-1/L1, FL, DLBCL, and MM) of approximately 30 participants per cohort treated with MK-7684A and the addition of Cohort G (relapsed/refractory: may include cHL or PMBCL previously treated with an anti-PD-1/L1, FL, DLBCL, and MM) of approximately 30 participants treated with vibostolimab monotherapy. The decision to open expansion cohorts in Part 2 will depend on the benefit and risk profile observed in Part 1.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Part 1: Cohorts A to F	MK-7684A	Vibostolimab 200mg+ pembrolizumab 20 mg/ 20mL vial	200 mg/ 200 mg	IV Infusion	Q3W up to 35 cycles	Test Product

Other current or former name(s) or alias(es) for study intervention(s) are as follows: MK-7684A is a coformulation of vibostolimab and pembrolizumab.

Total Number of Intervention Groups/Arms	Part 1: Cohorts A to F will be treated with MK-7684A coformulation
Duration of Participation	Each participant will participate in the study from the time that the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of 28 days, each participant will be assigned to receive study intervention until 1 of the conditions for discontinuation of study intervention is met (as defined in Section 7.1), or until the participant has received 35 administrations of MK-7684A. All participants who achieve a CR may be eligible for a second course of treatment (up to an additional 17 cycles of MK-7684A) if there is an investigator-determined disease progression as per disease-specific criteria after initial treatment or first course has been completed or stopped for confirmed CR. After the approval of Amendment 5, the study will end 90 days after the last participant completes 35 cycles of treatment, or terminates early, whichever comes first, and second course option for treatment is no longer available. Participants in the Imaging Follow-up or Survival

	Follow-up phase will be discontinued from the study and no further imaging or participant contacts will be required. After the end-of-study treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described under Section 8.4.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Steering Committee	No

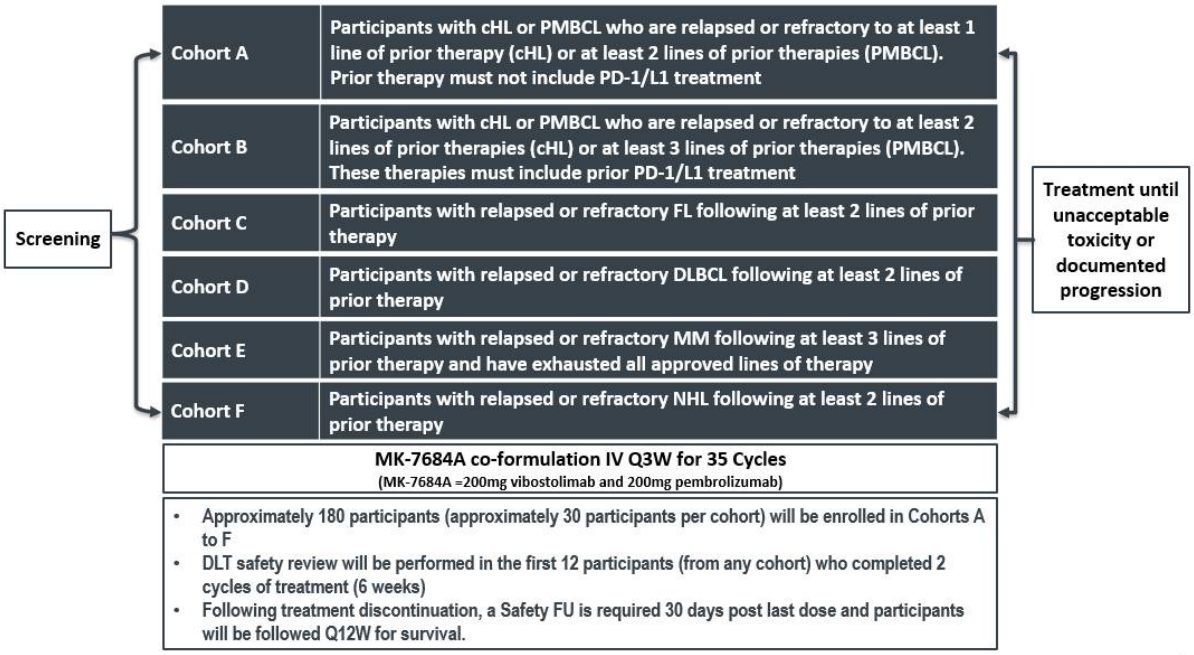
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 10.

1.2 Schema

The study design for Part 1 is depicted in Figure 1 and for Part 2 in Figure 2.

Figure 1 Signal Finding (Part 1)



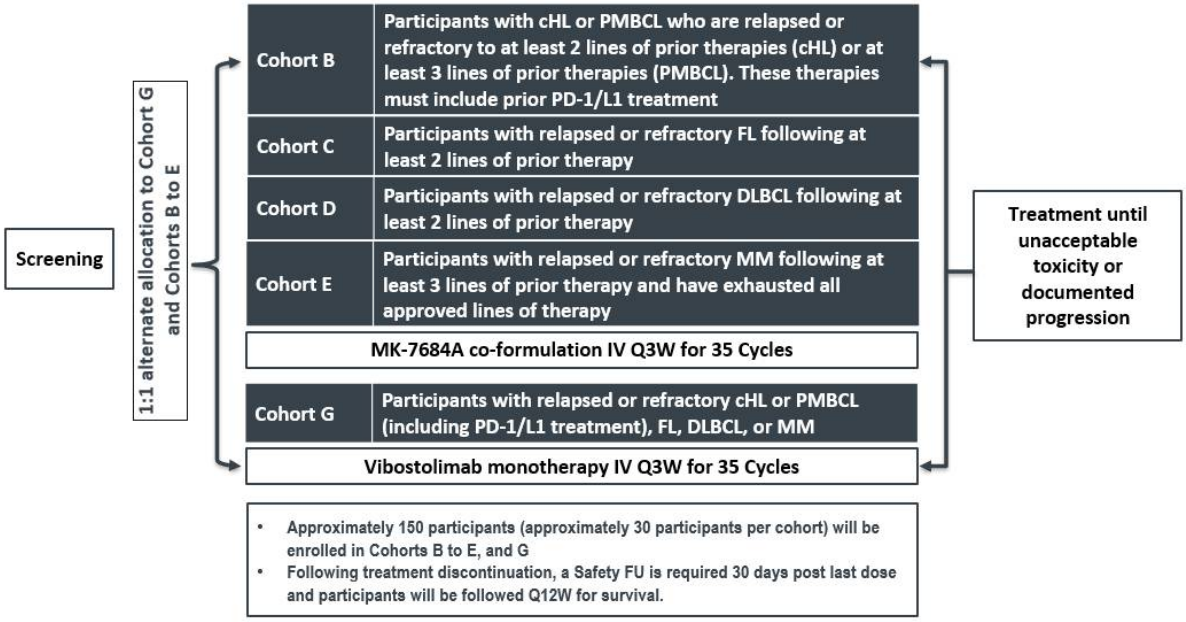
In addition to the number of prior lines of therapies specified in the schema, requirements regarding stem cell transplant are described in Section 5.1.

Abbreviations: cHL=classic Hodgkin's lymphoma; DLBCL=diffuse large B-cell lymphoma; FL=Follicular lymphoma; FU=follow-up; IV=intravenous; MM=multiple myeloma; NHL=non-Hodgkin's lymphoma; PD-1/L1=programmed cell death protein 1/ligand 1; PMBCL=primary mediastinal B - cell lymphoma; Q3W=every 3 weeks; Q12W=every 12 weeks.

Note: After approval of Amendment 5, participants will not be offered second course treatment. The study will end 90 days after the last participant completes 35 cycles of treatment, or terminates early, whichever comes first and second course option for treatment is no longer available. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study and no further imaging or participant contacts will be required.

Figure 2 Cohort Expansion (Part 2)

The decision to open expansion cohorts in Part 2 will depend on the benefit and risk profile observed in Part 1.



In addition to the number of prior lines of therapies specified in the schema, requirements regarding stem cell transplant are described in Section 5.1.

Abbreviations: cHL=classic Hodgkin's Lymphoma; DLBCL=Diffuse Large B-cell Lymphoma; FL=Follicular Lymphoma; FU=follow-up; IV=intravenous; MM=Multiple Myeloma; PD-1/L1=programmed cell death protein 1/ligand 1; PMBCL=Primary mediastinal B - cell Lymphoma; Q3W=every 3 weeks; Q12W=every 12 weeks.

Note: After approval of Amendment 5, participants will not be offered second course treatment. The study will end 90 days after the last participant completes 35 cycles of treatment, or terminates early, whichever comes first and second course option for treatment is no longer available. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study and no further imaging or participant contacts will be required.

1.3 Schedule of Activities

After approval of Amendment 5, participants will not be offered second course treatment. This will not affect participants already receiving the second course treatment.

The study will end 90 days after the last participant completes 35 cycles of treatment, or terminates early, whichever comes first and second course option for treatment is no longer available. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study and no further visits will be required.

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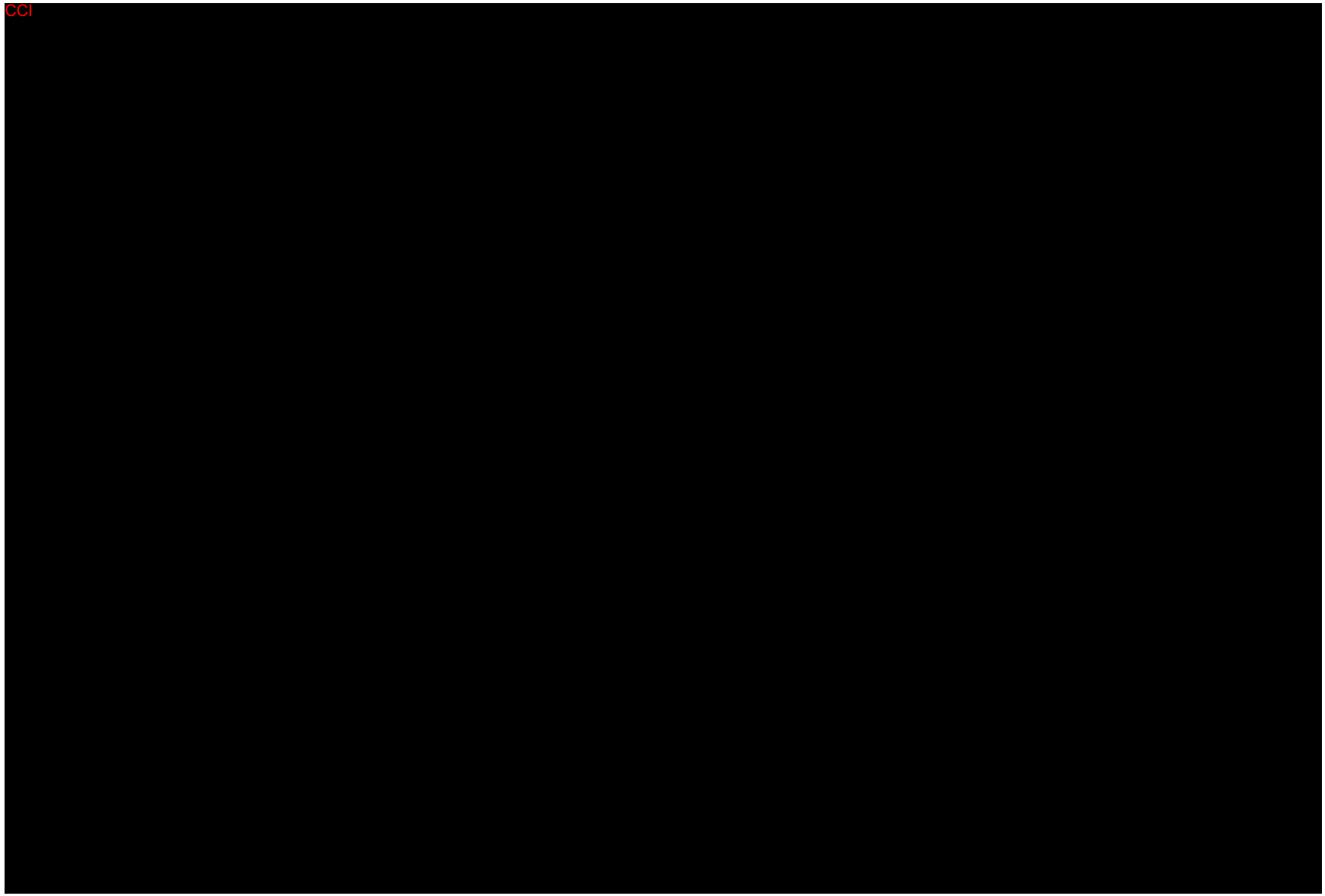

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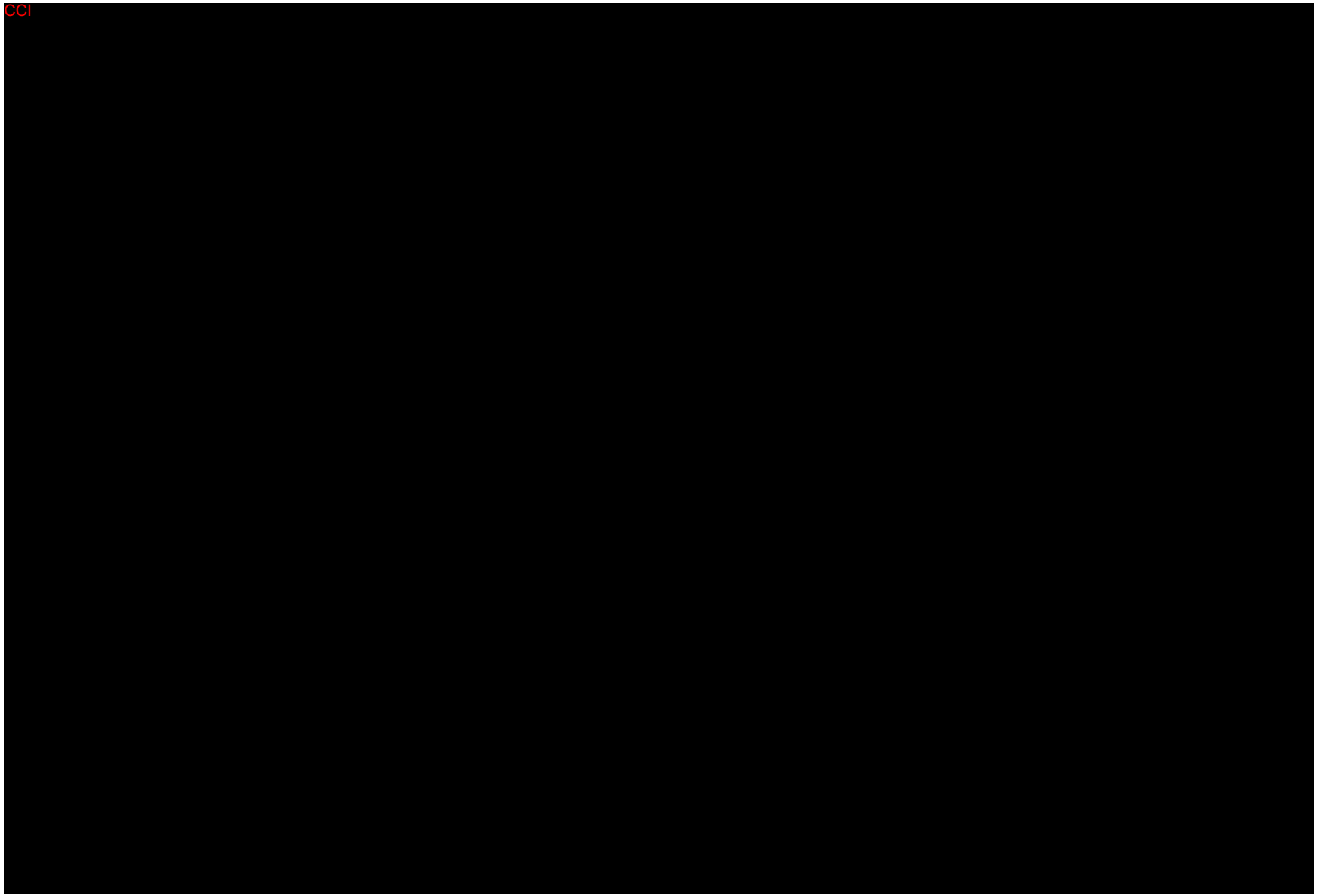

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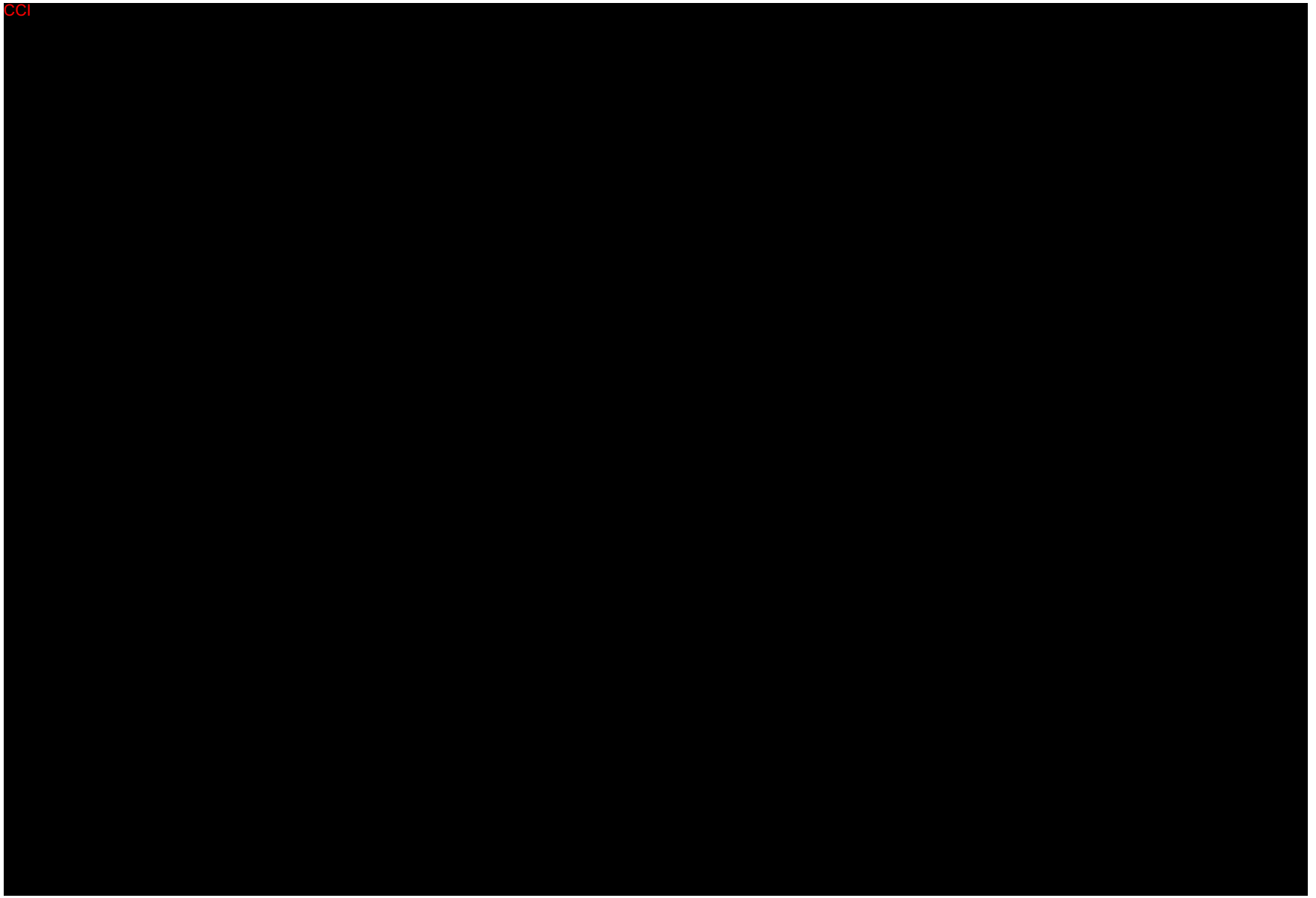

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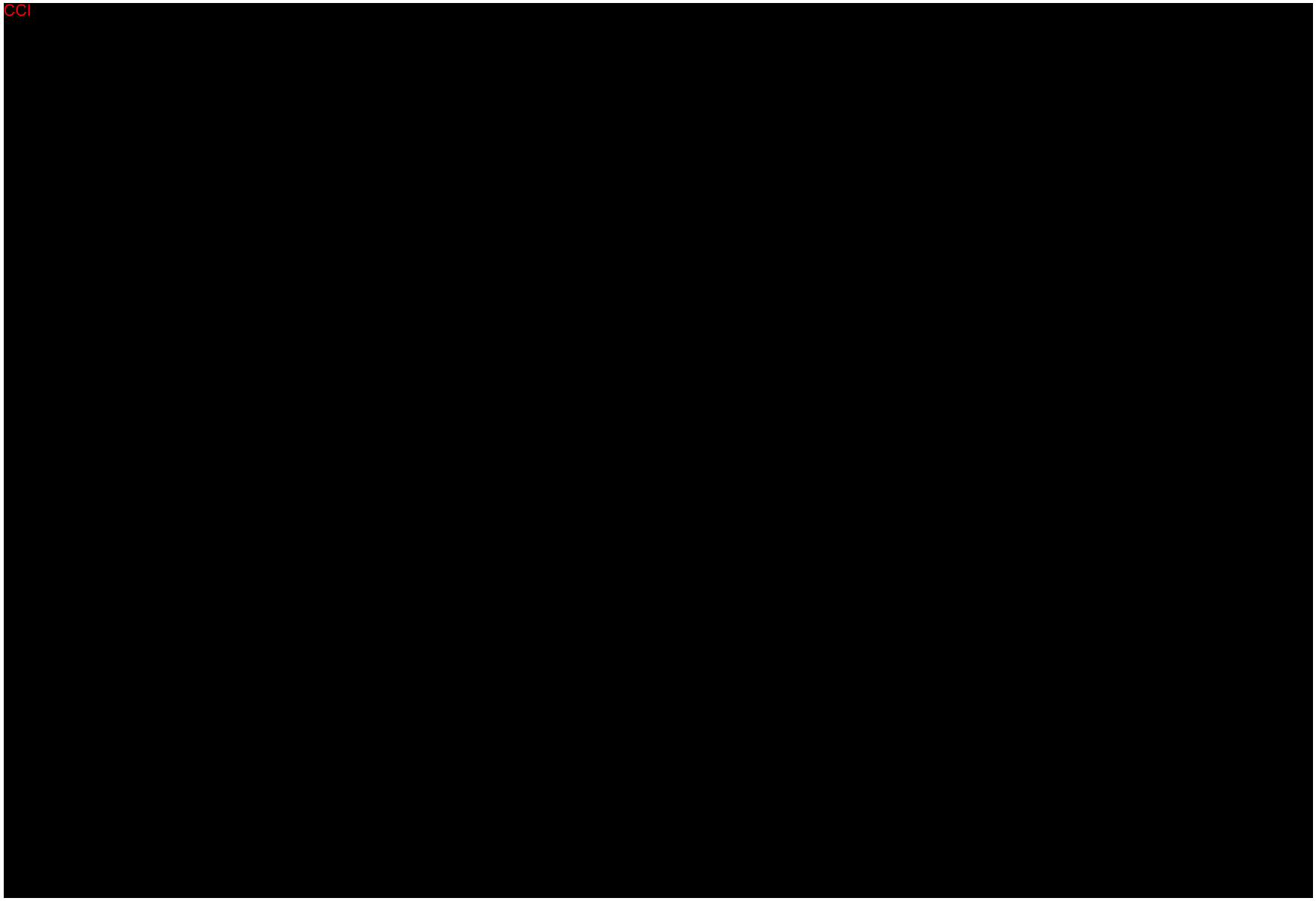
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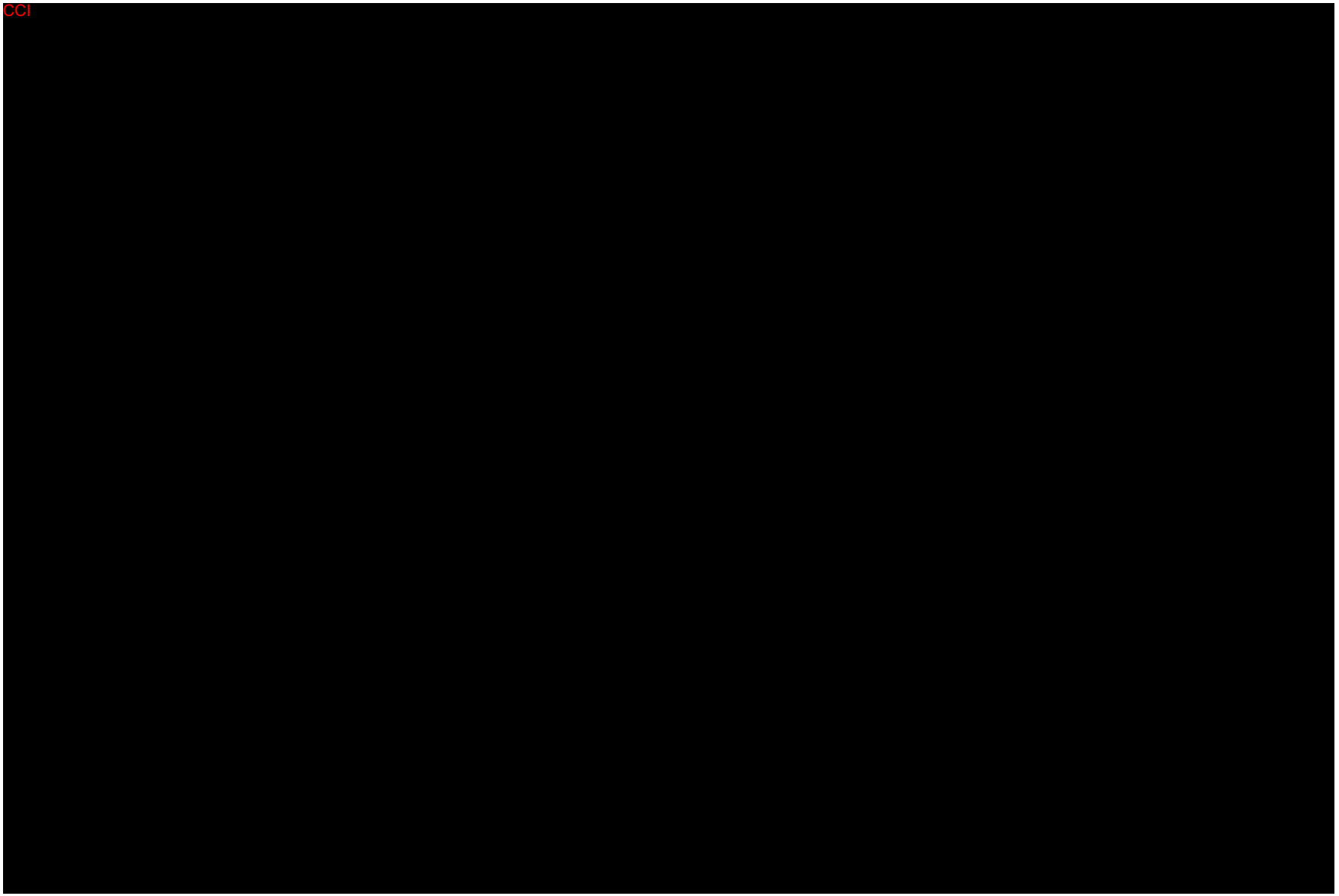

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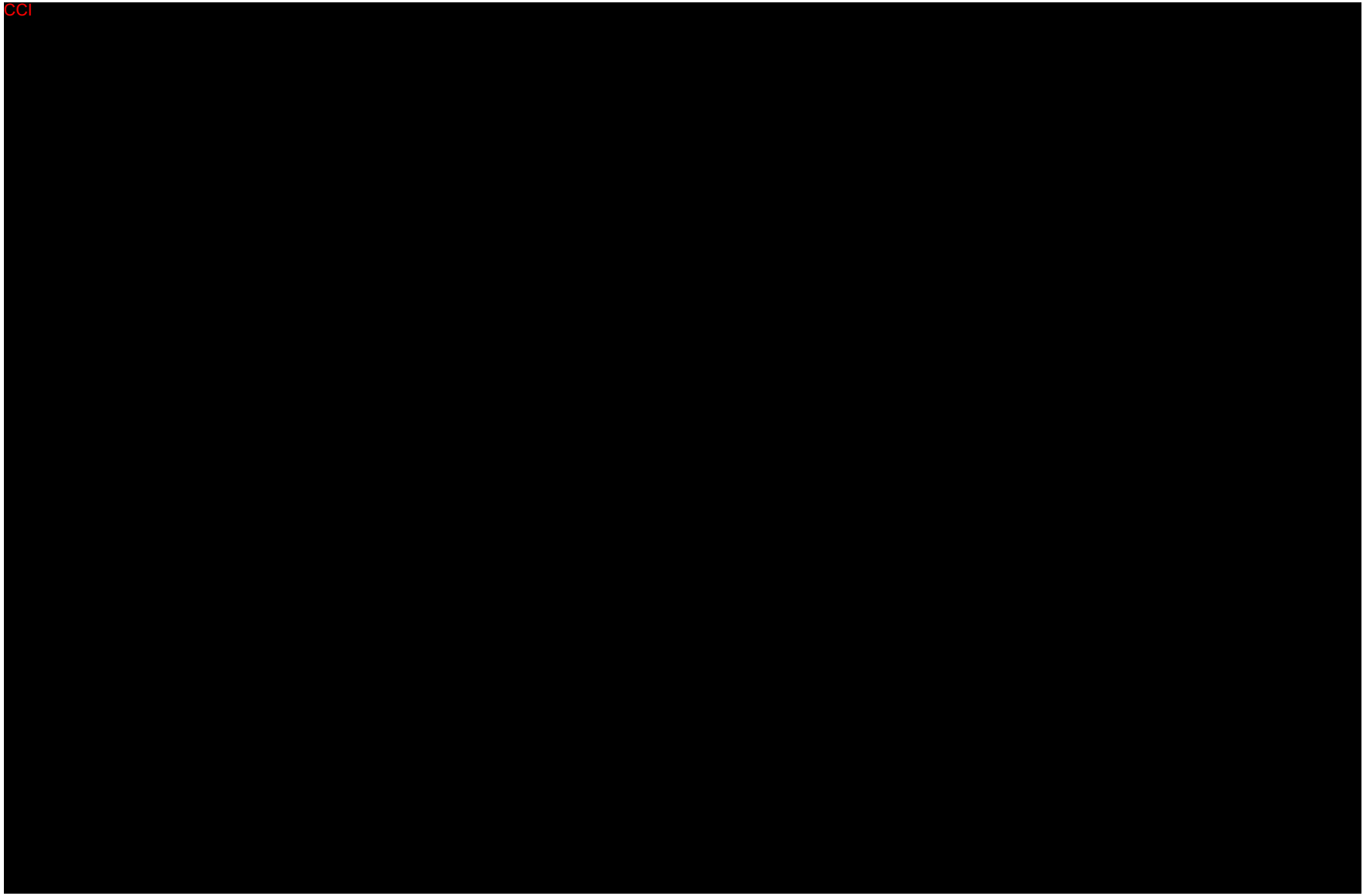

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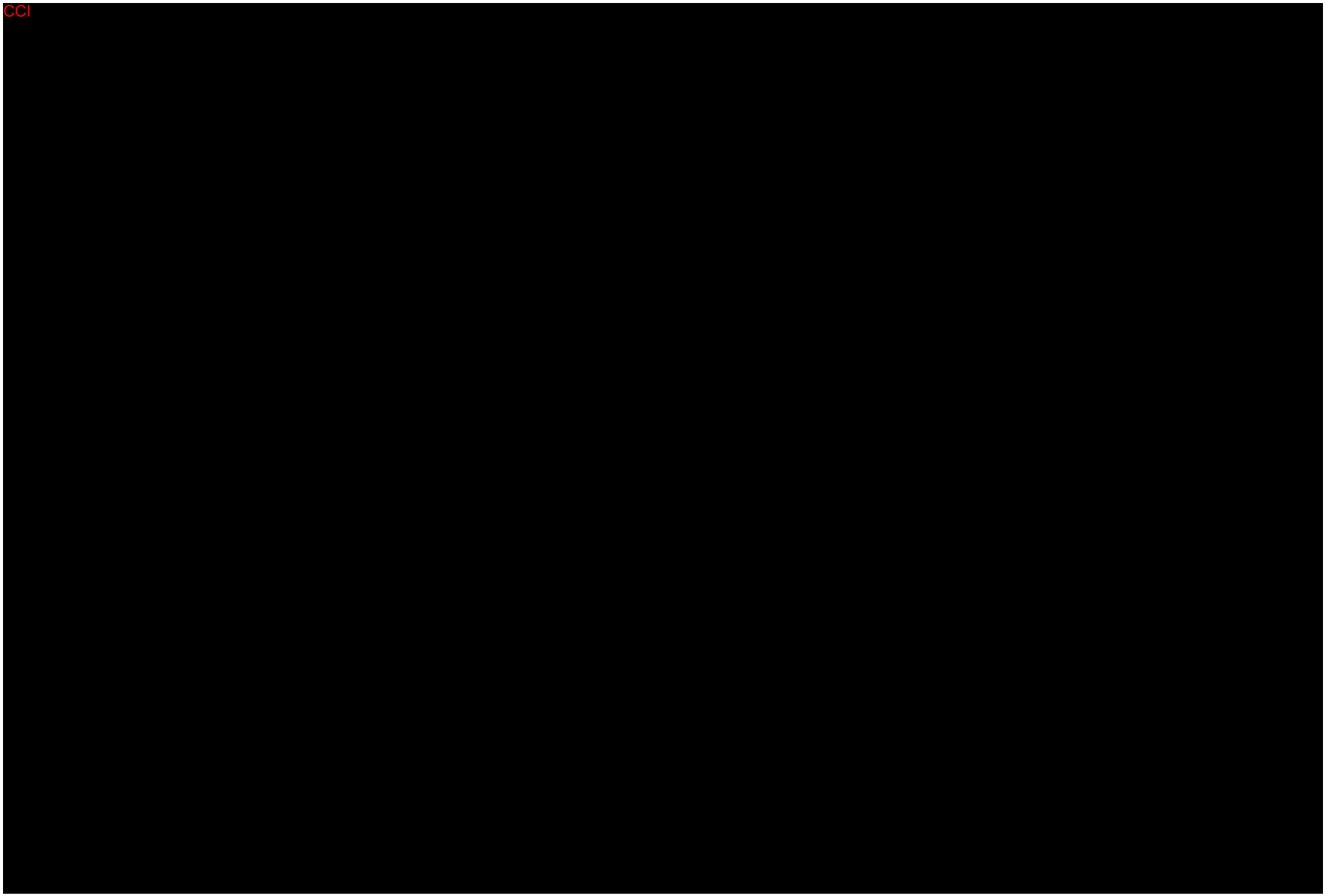

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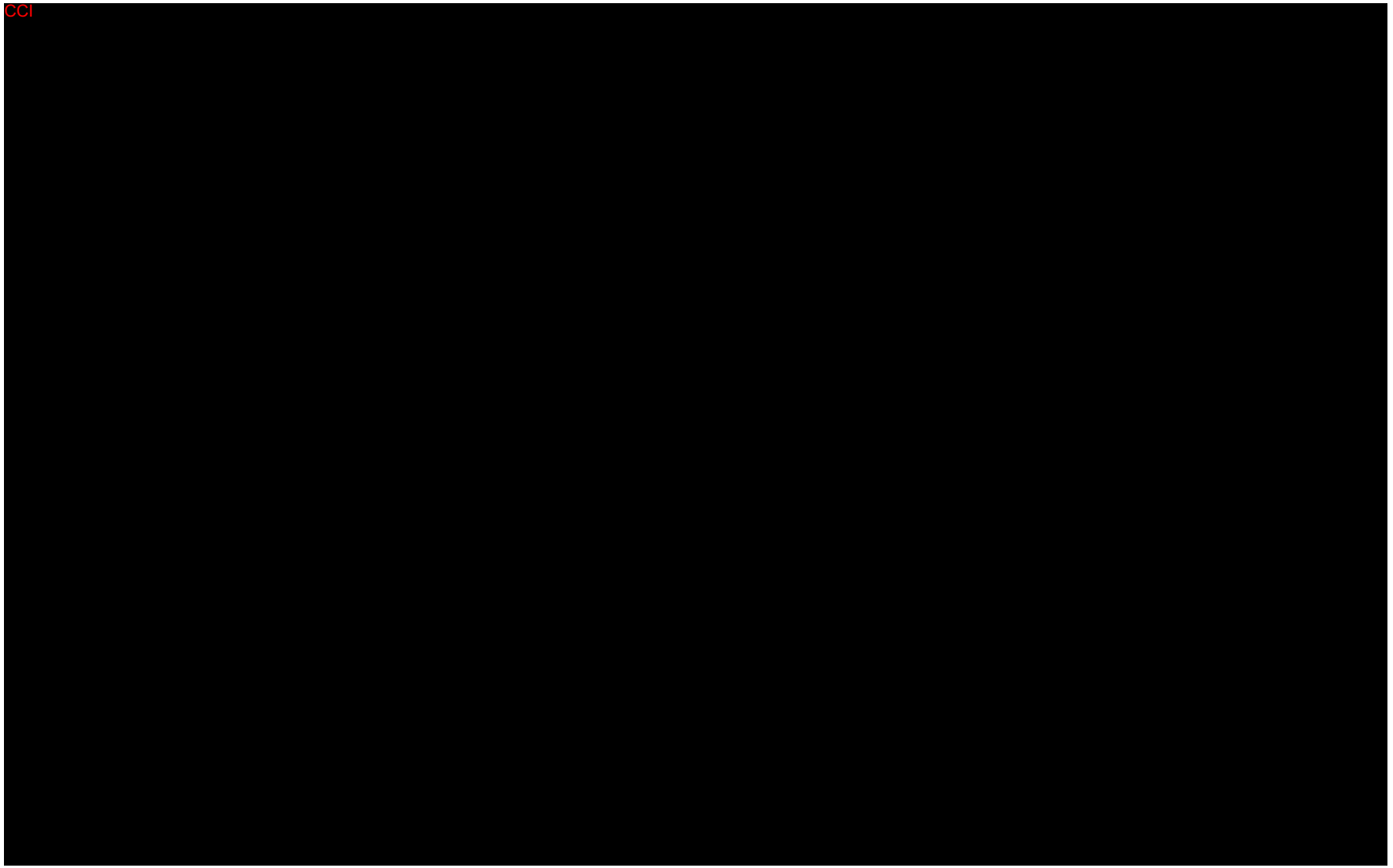

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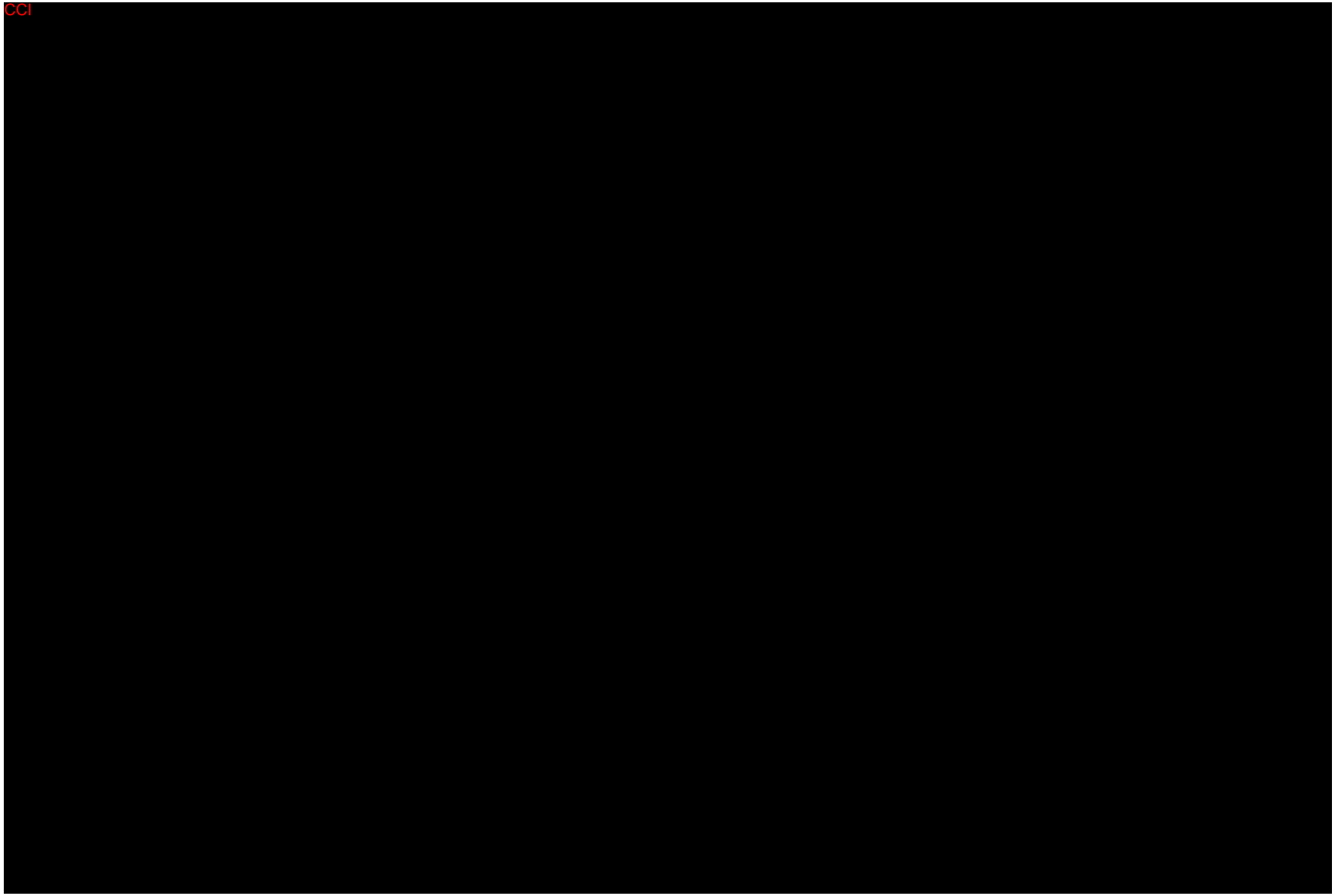
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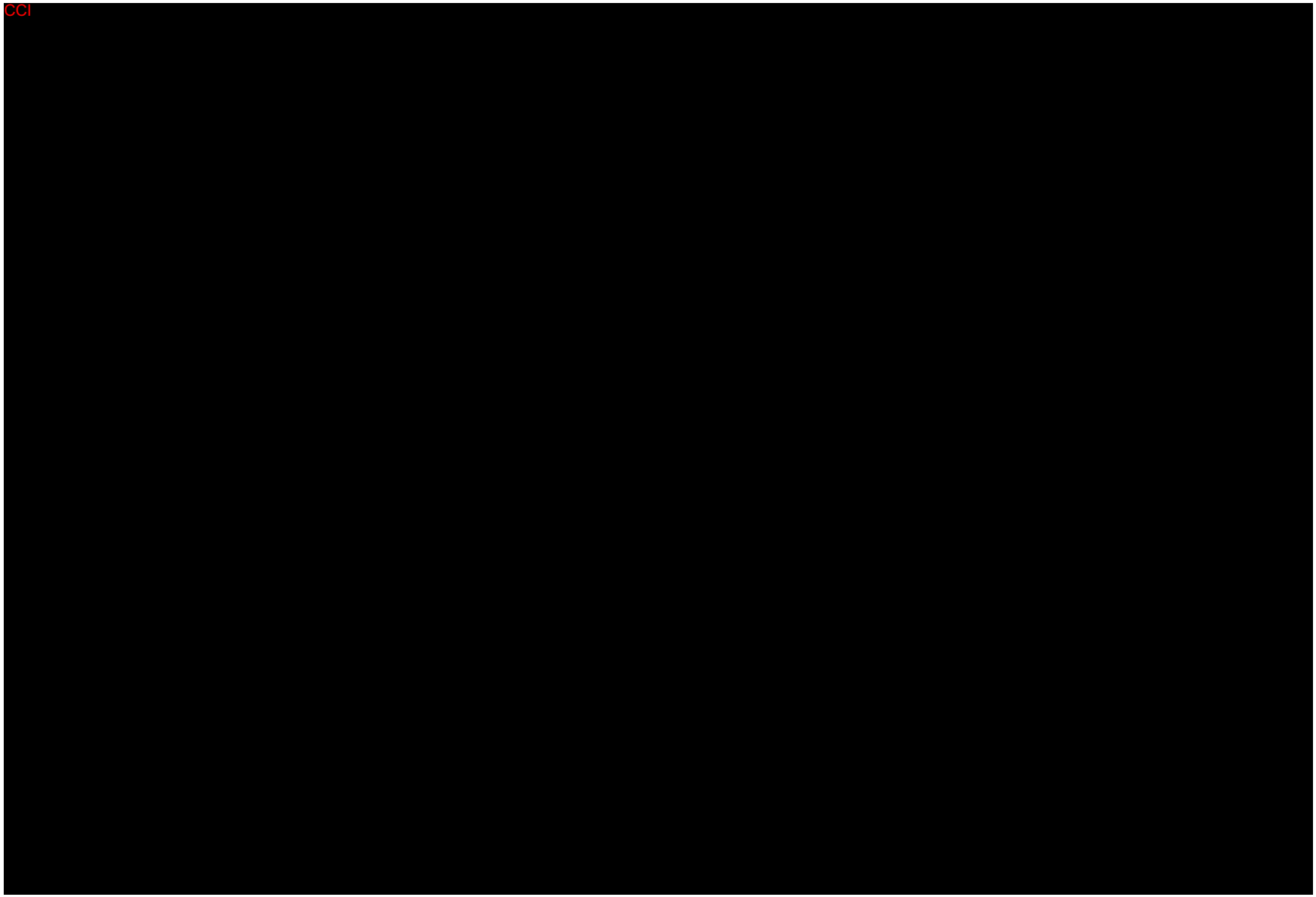

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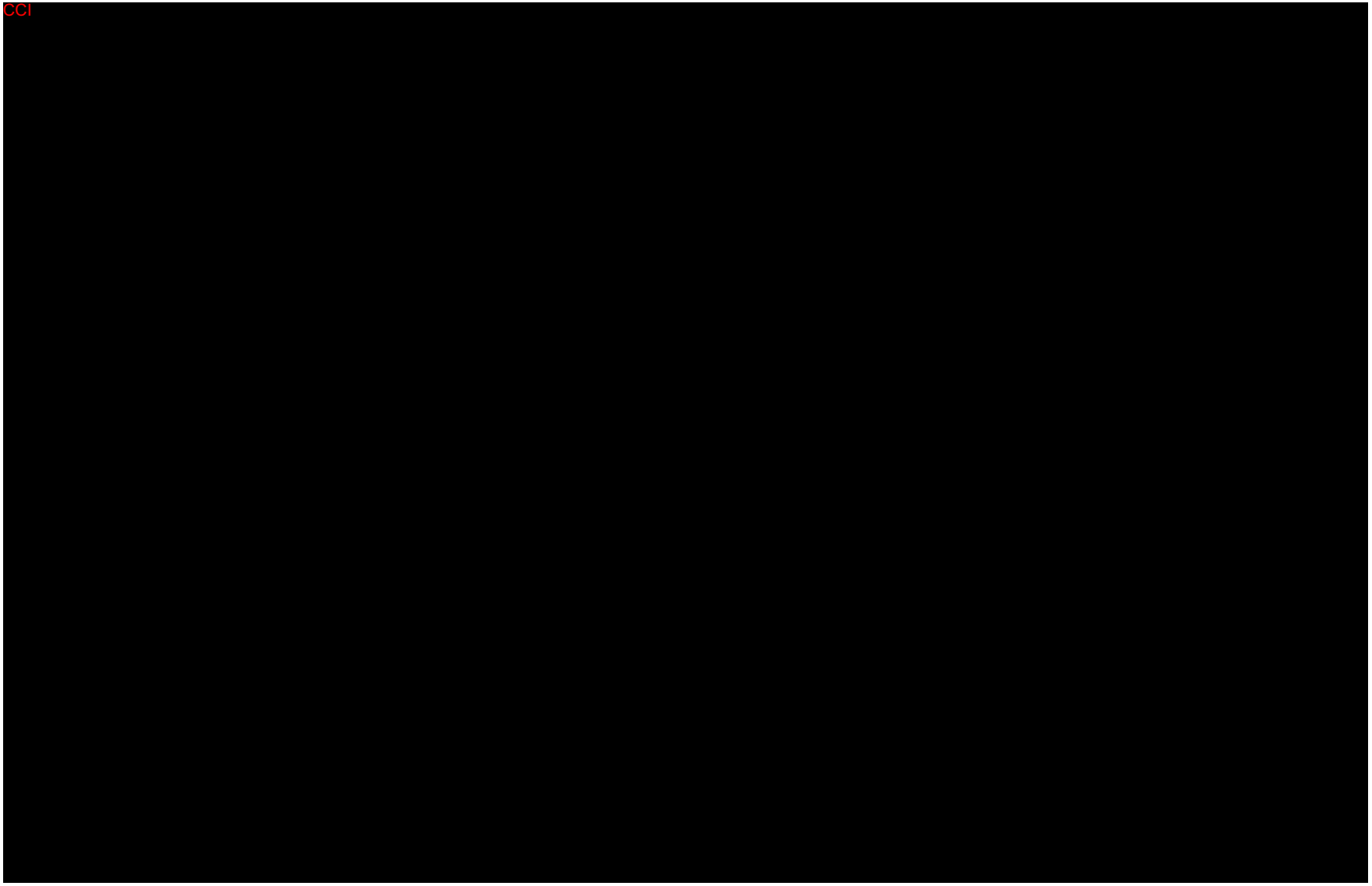

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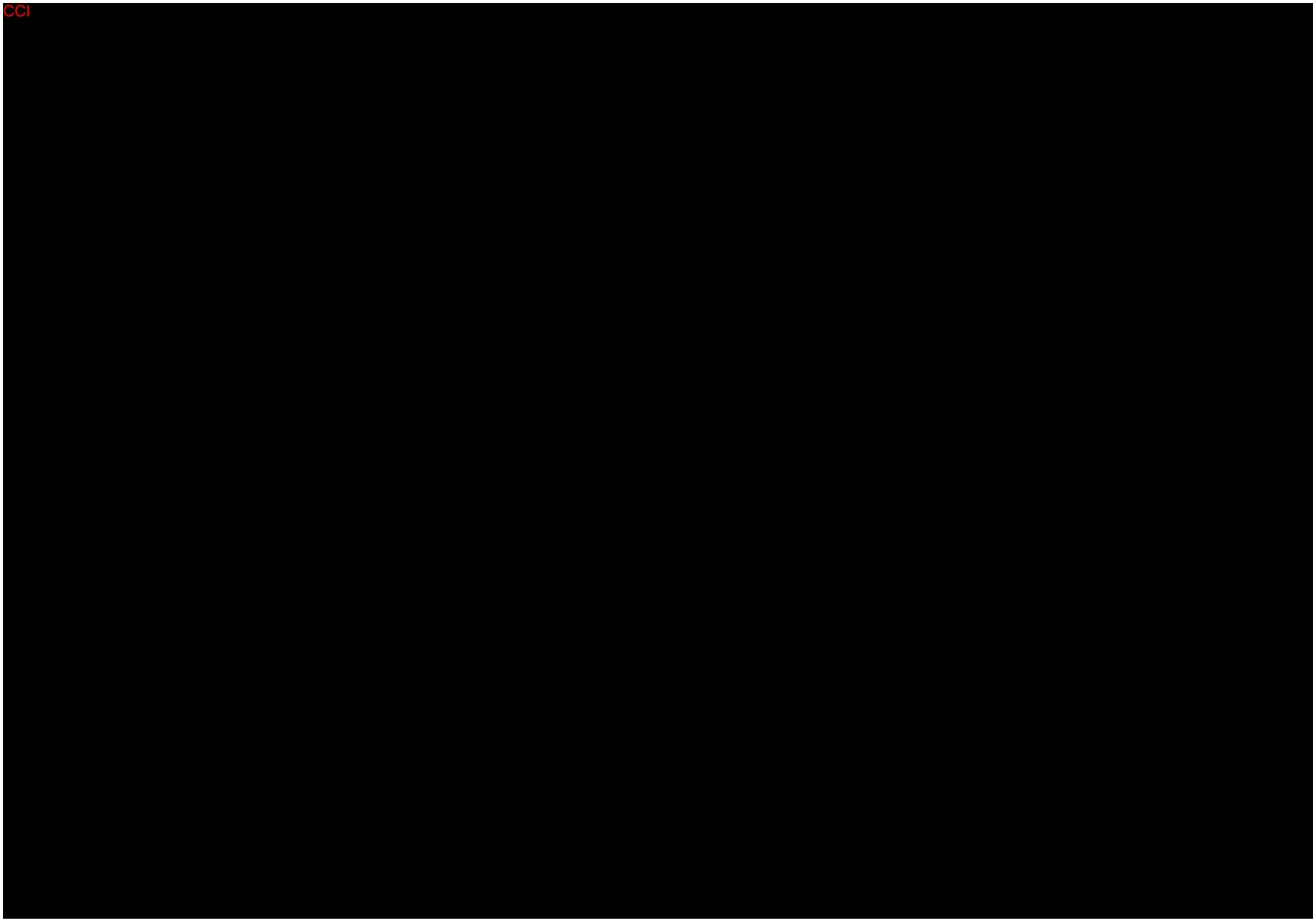

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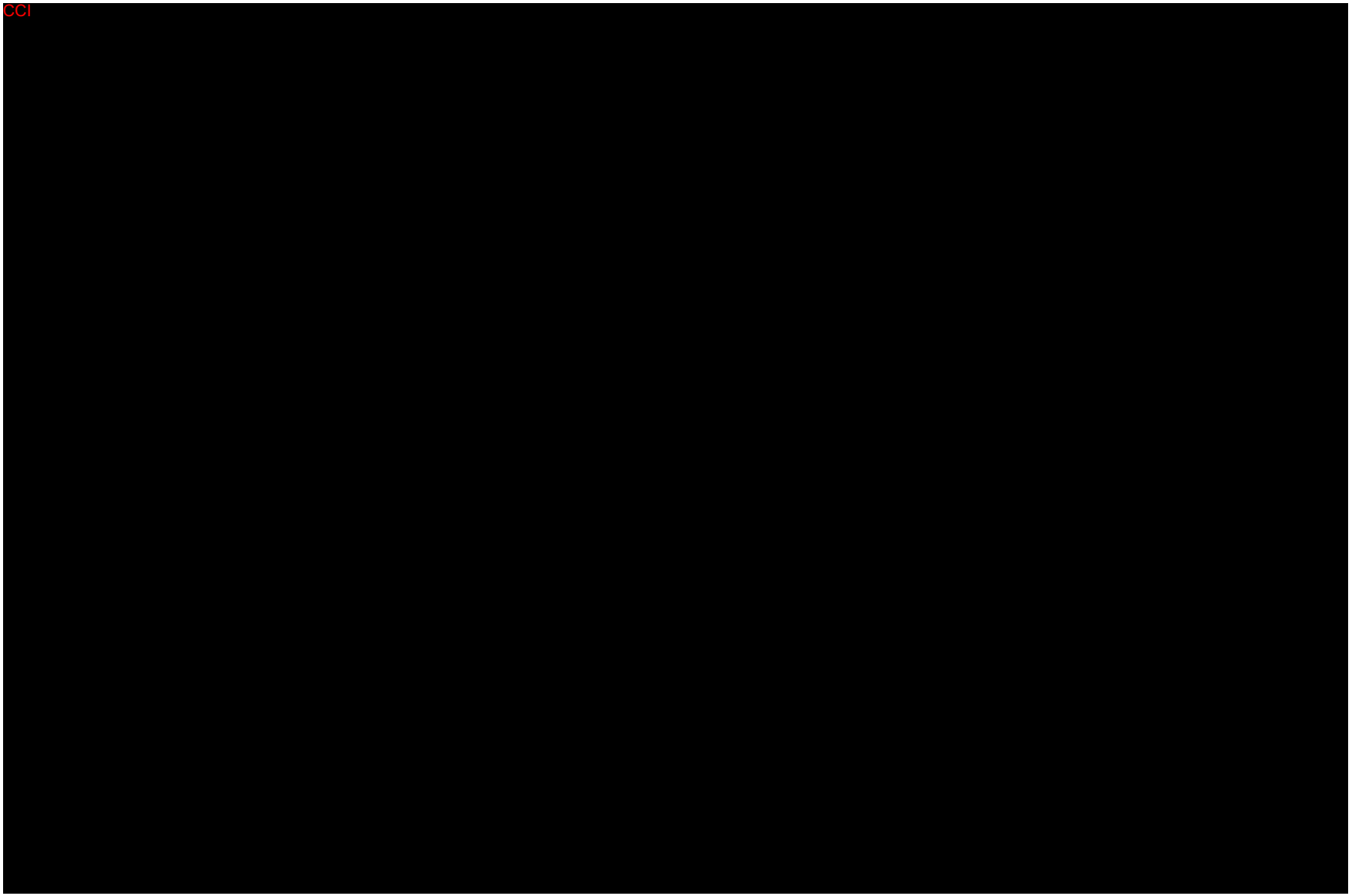

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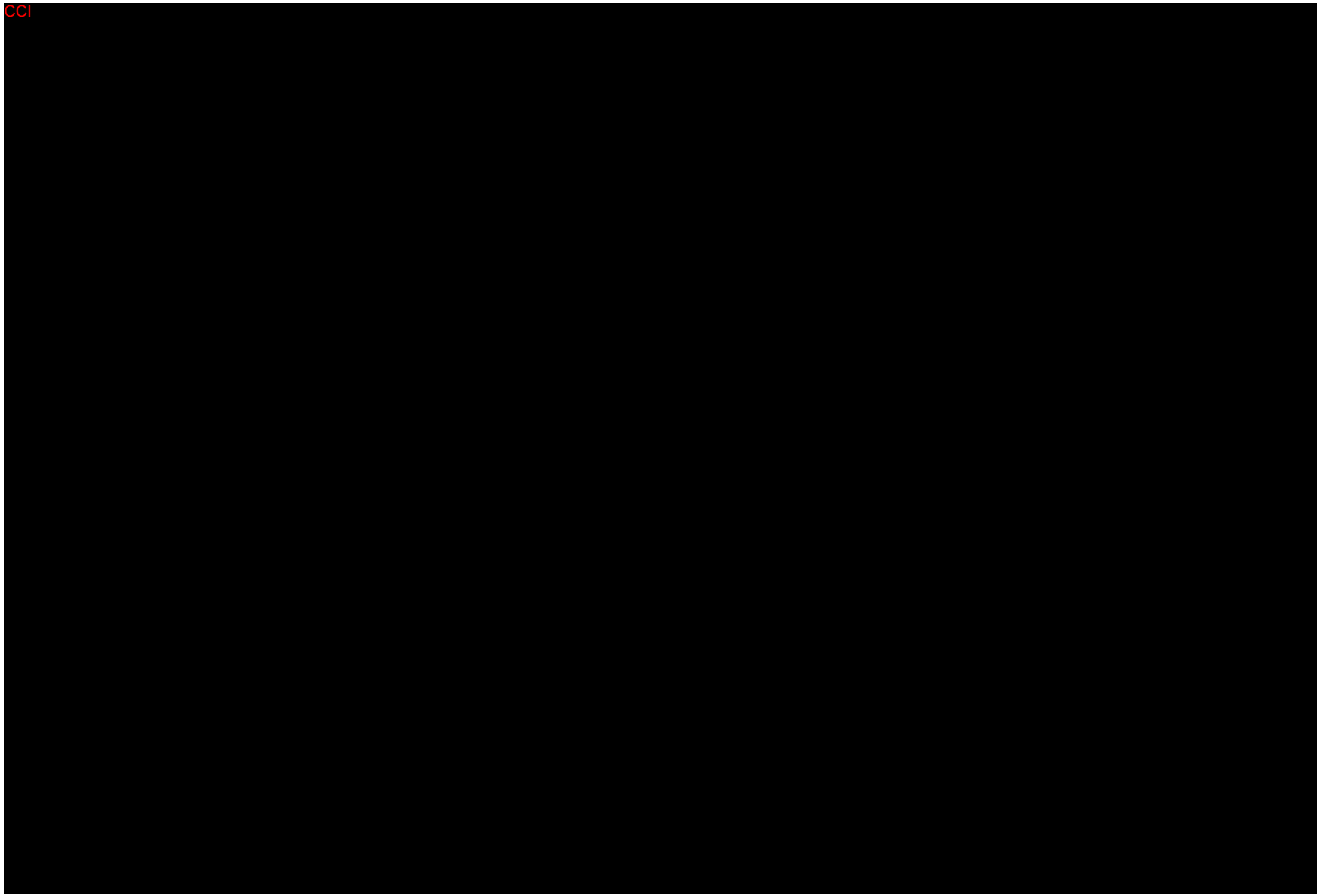

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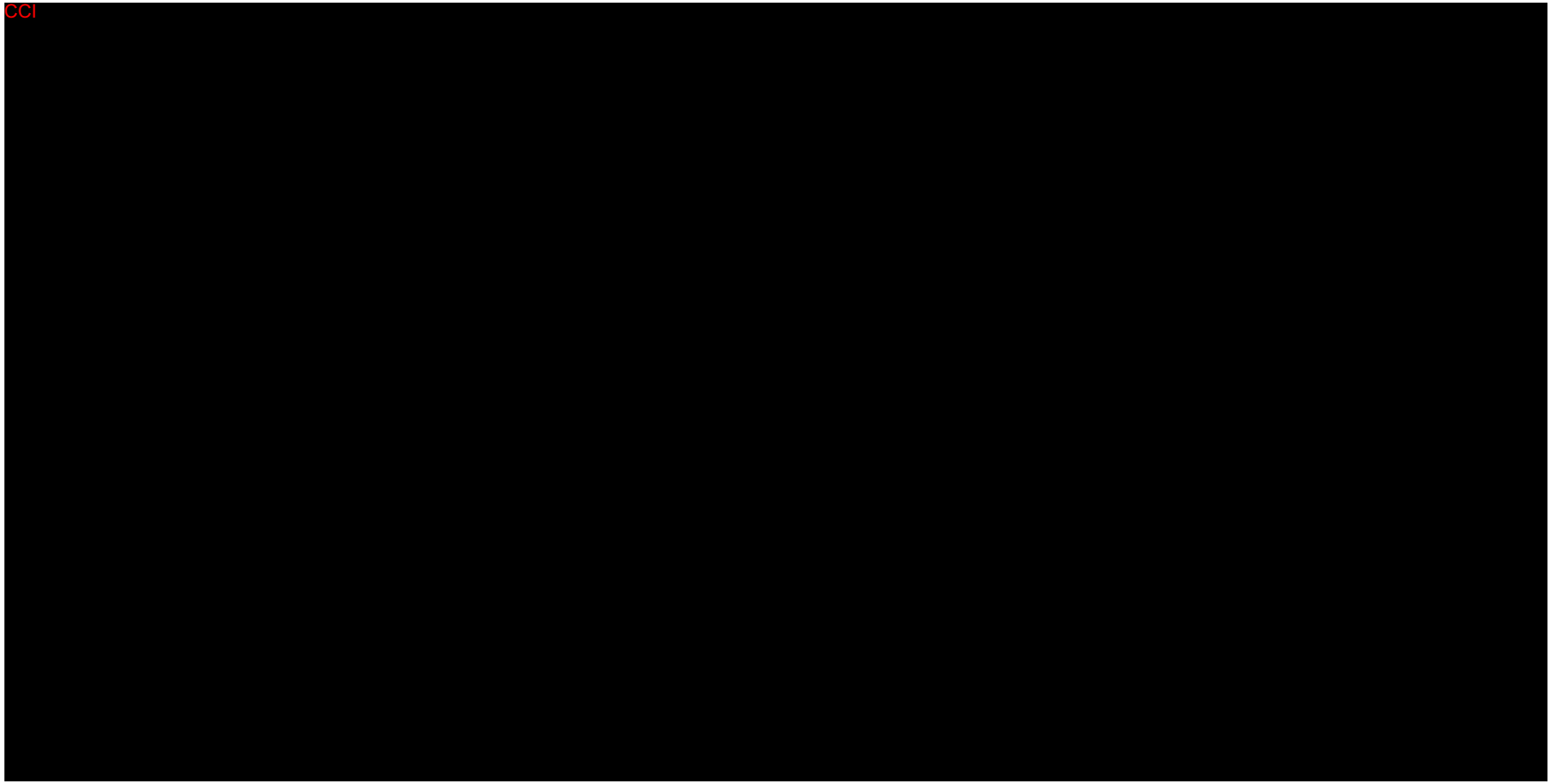

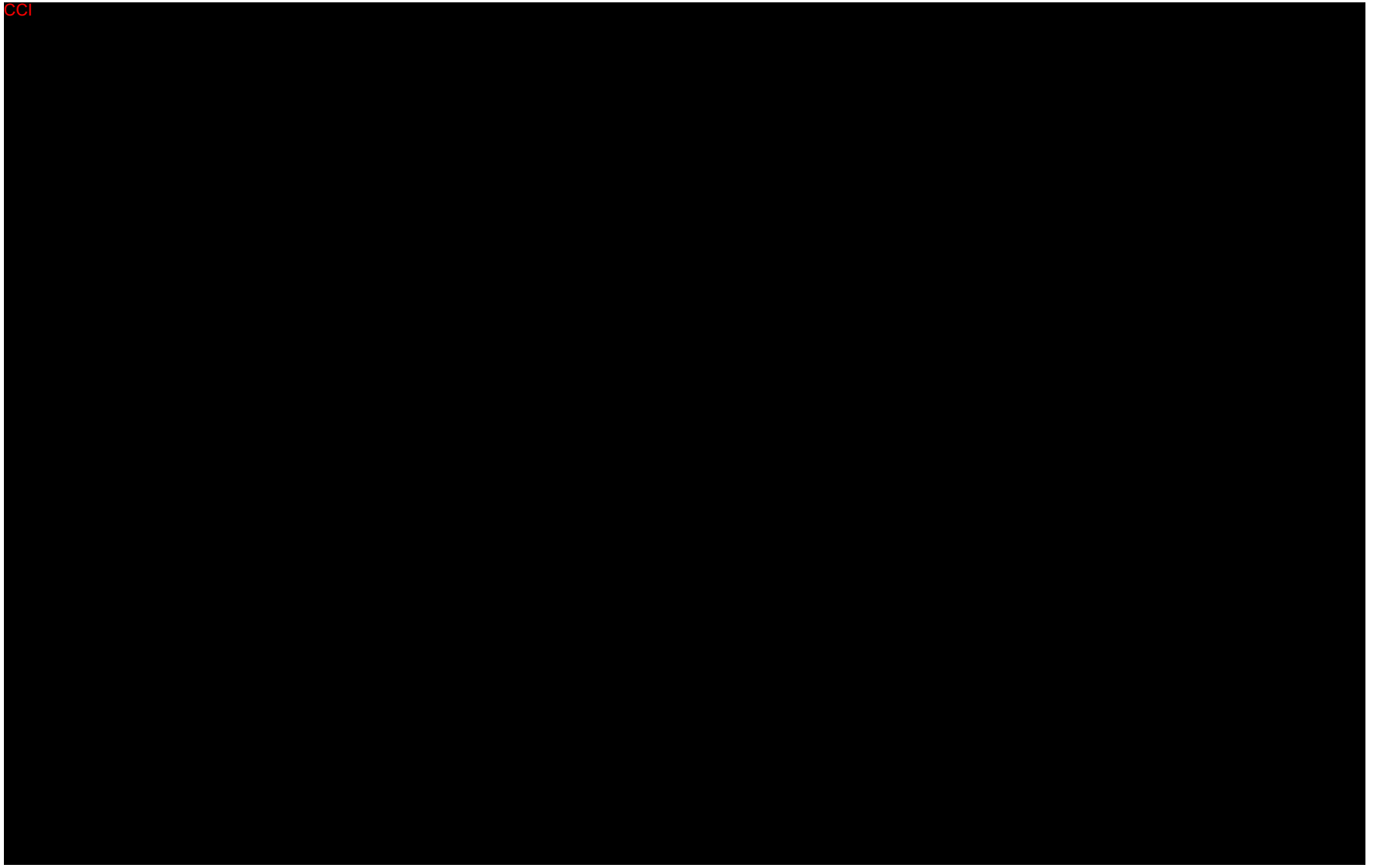
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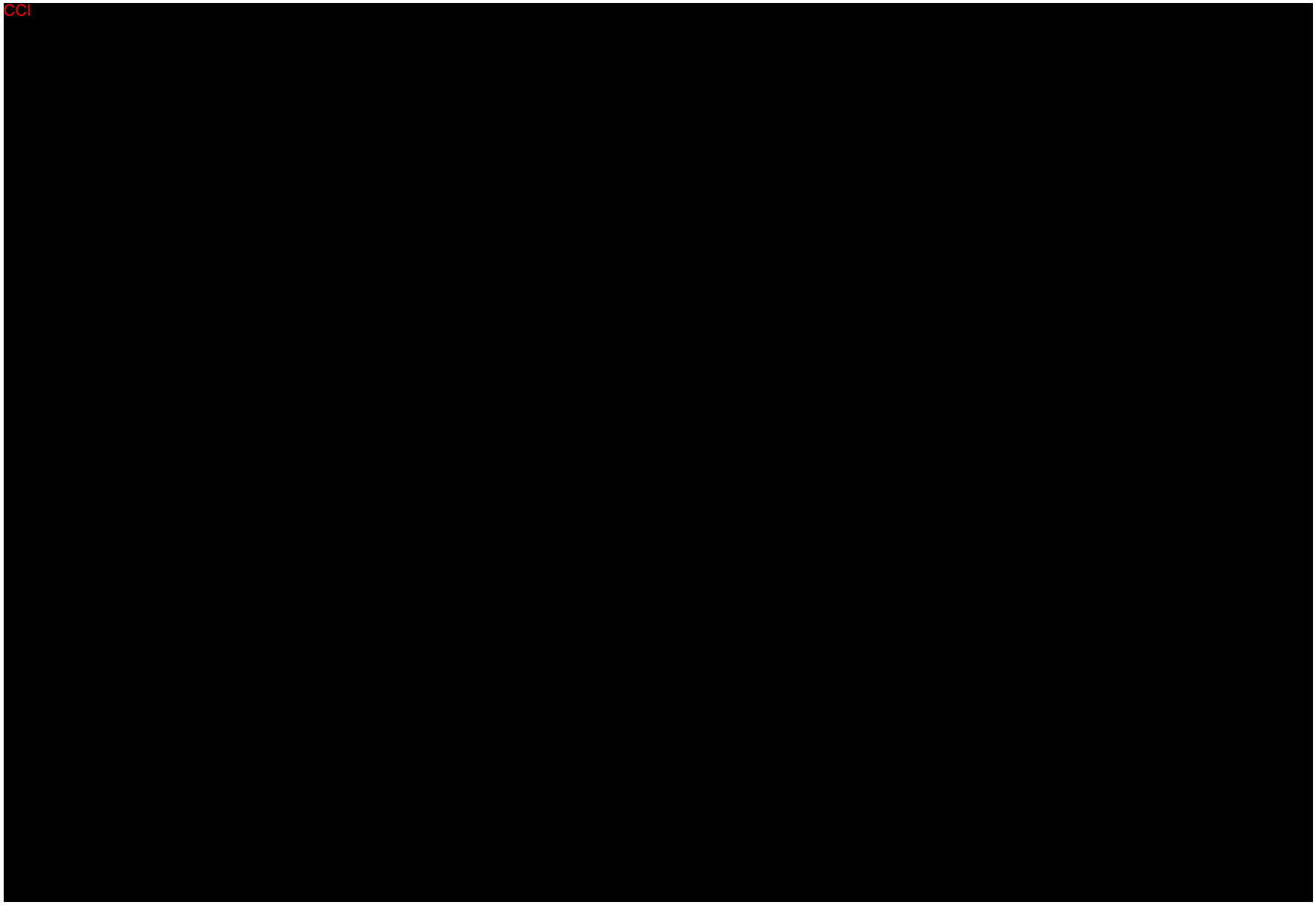

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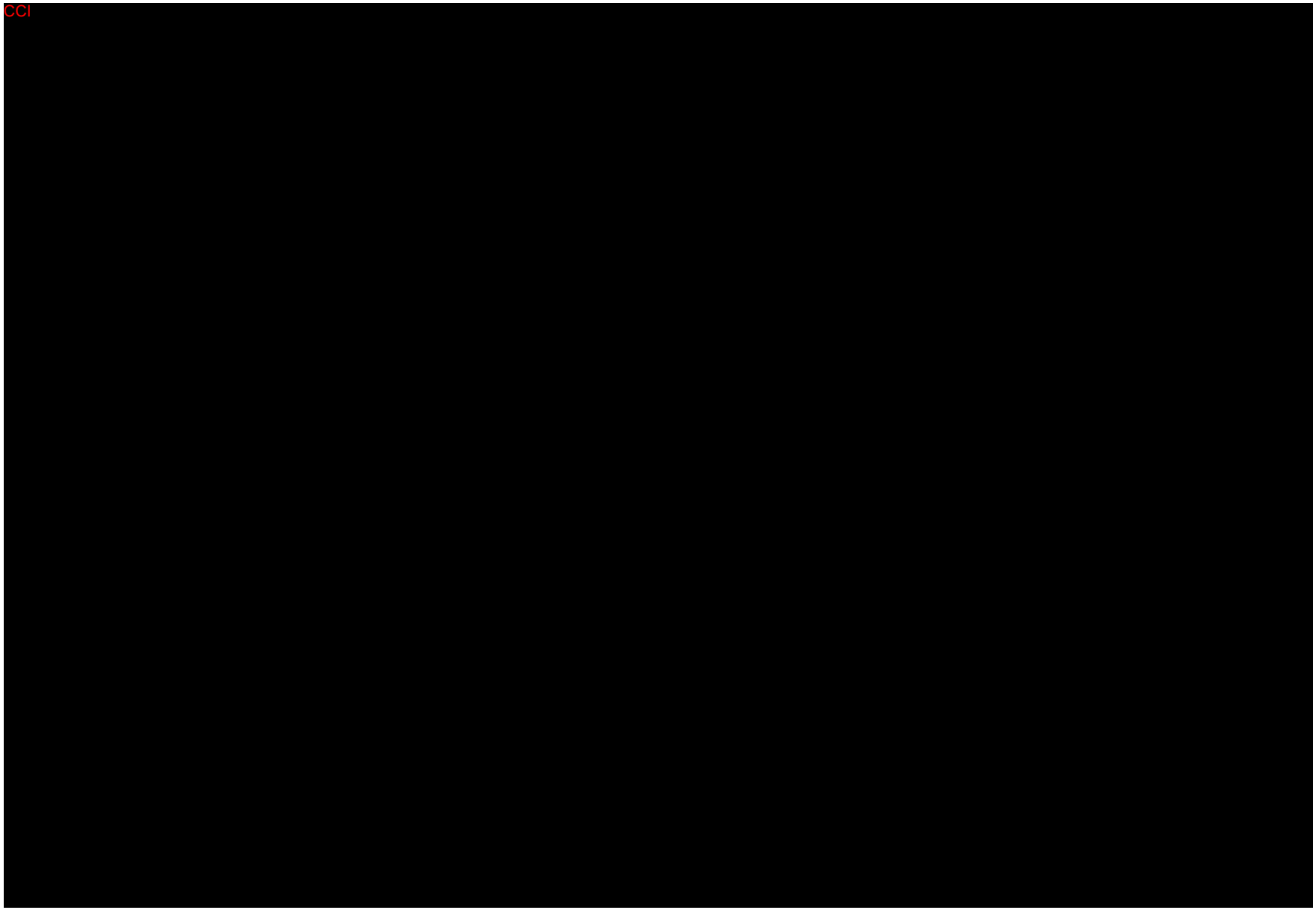

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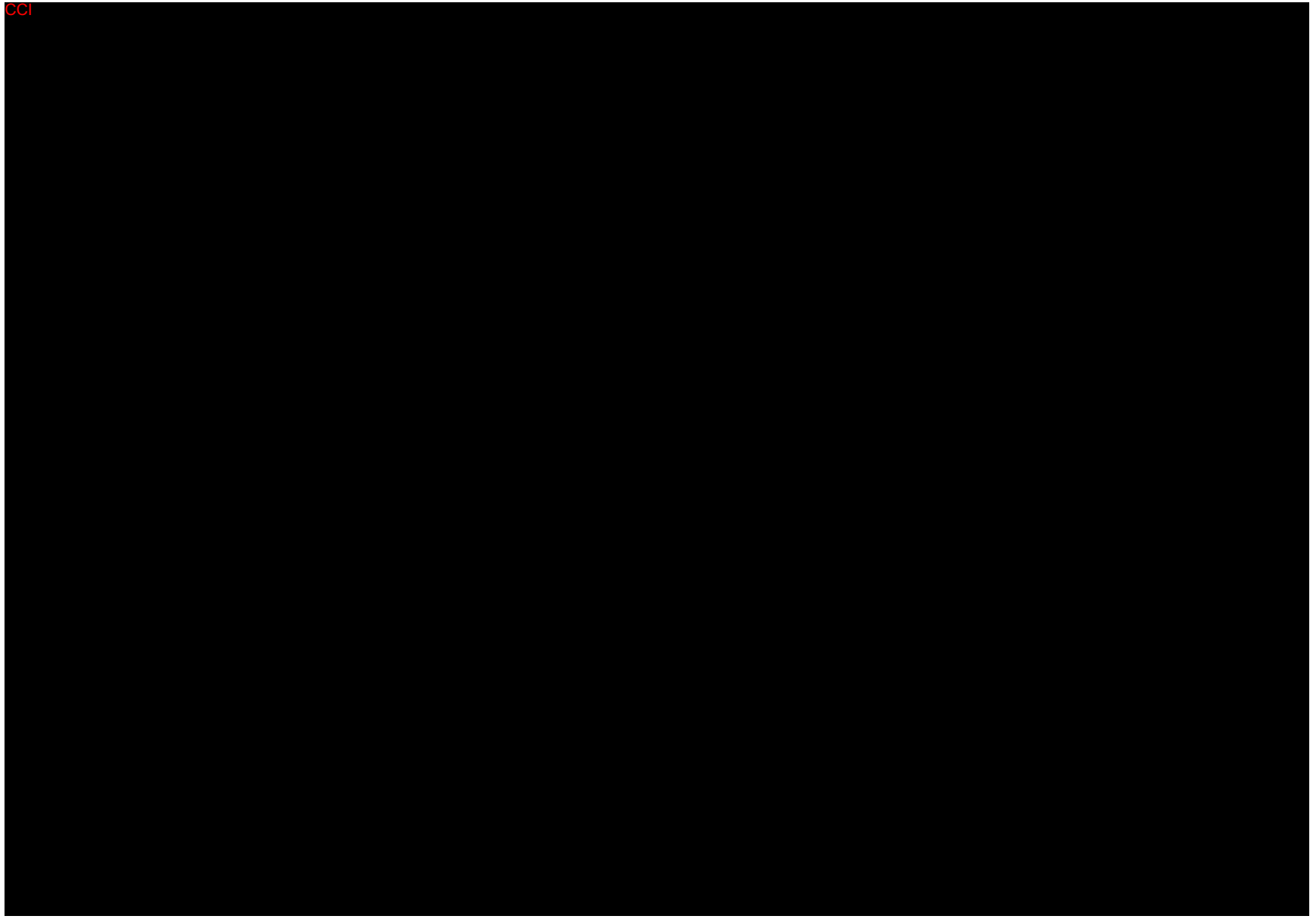

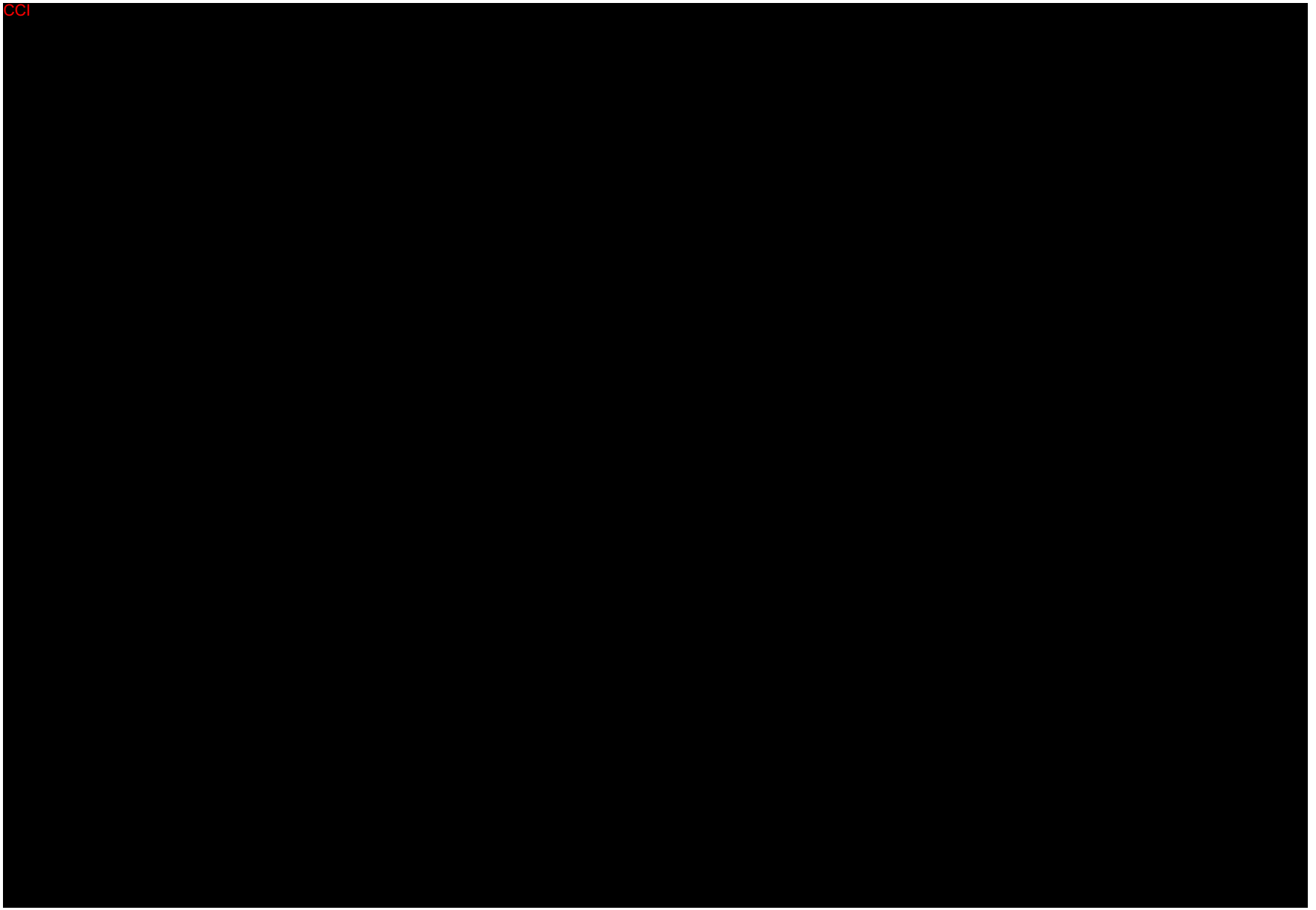
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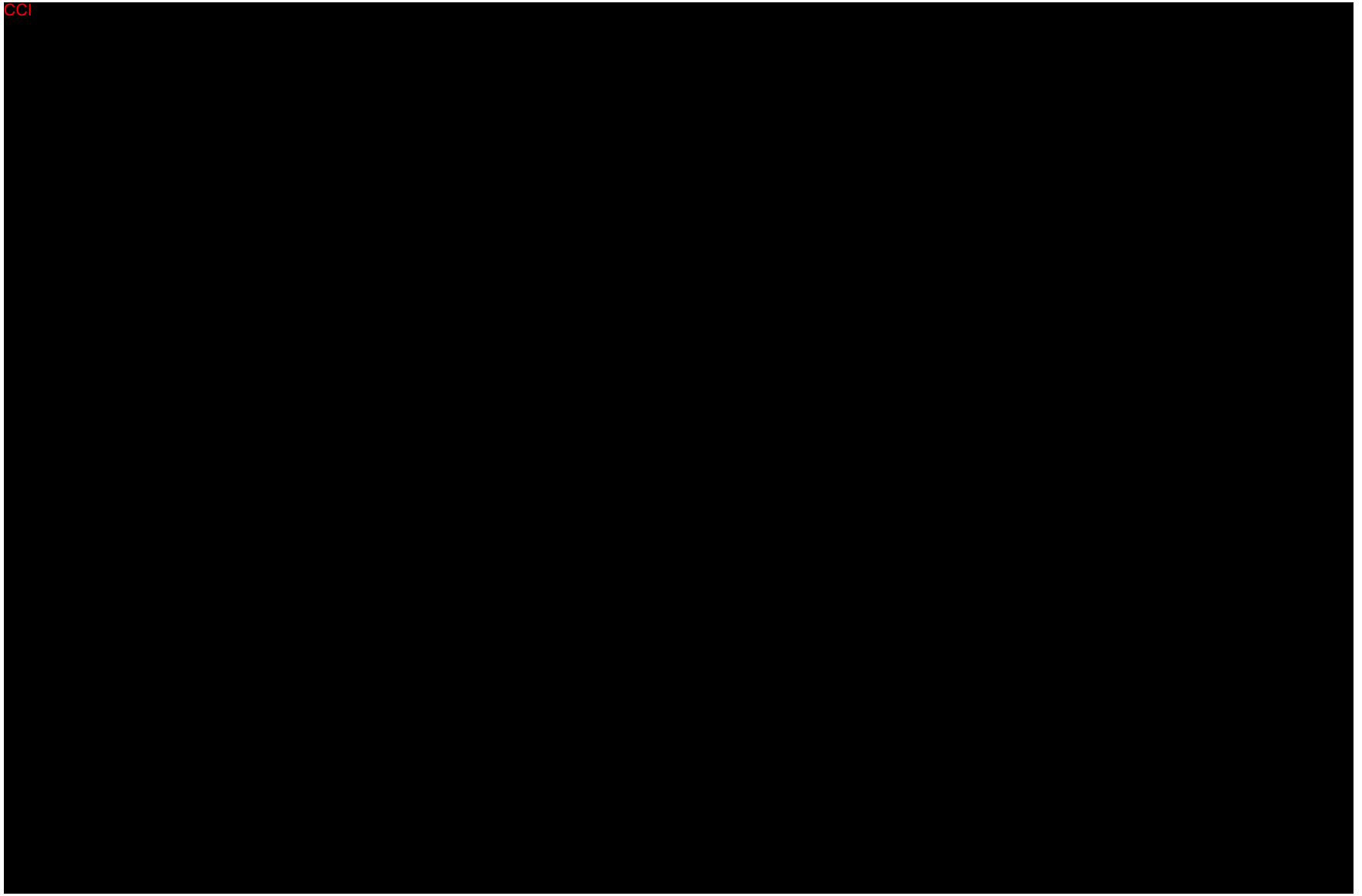

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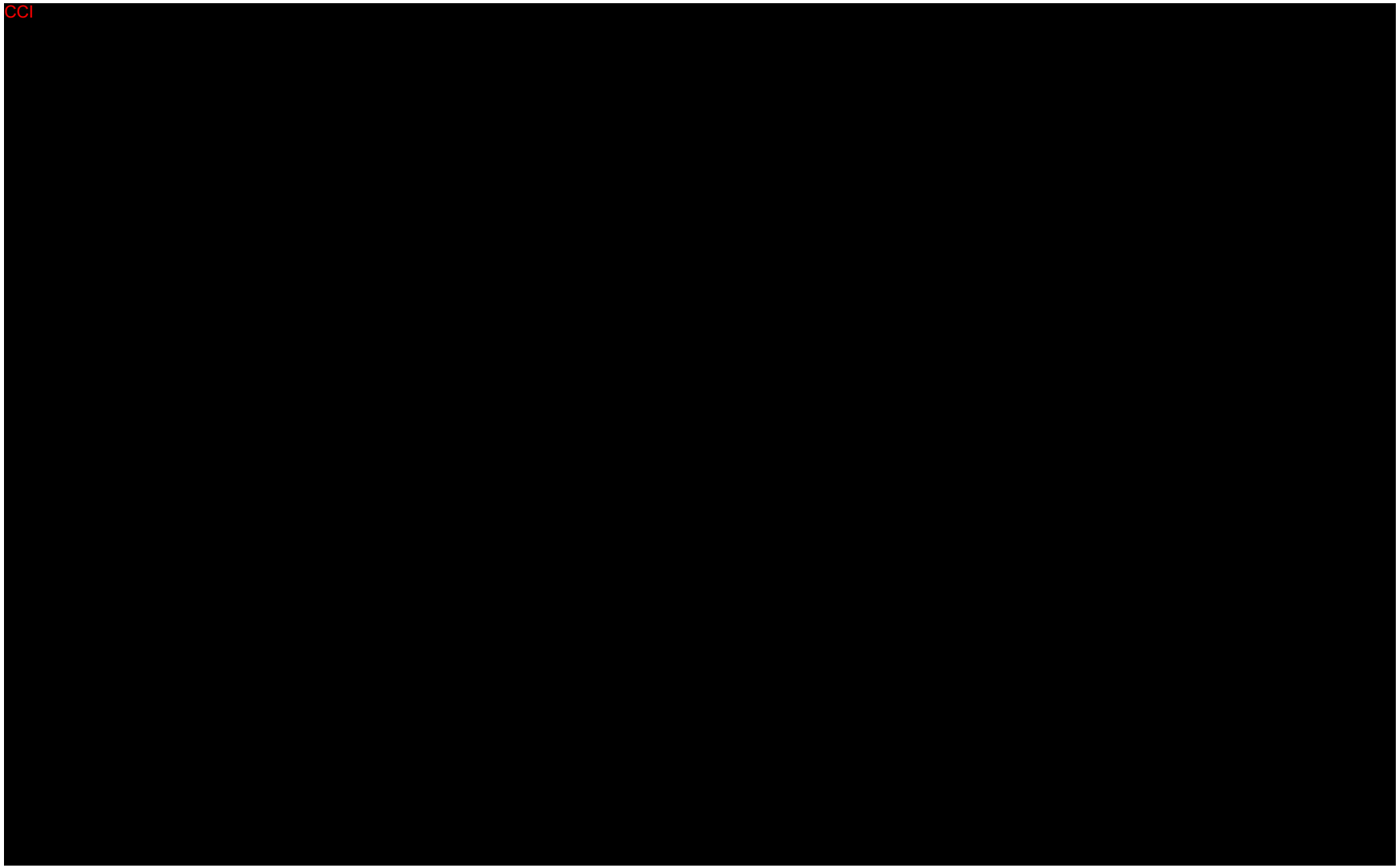

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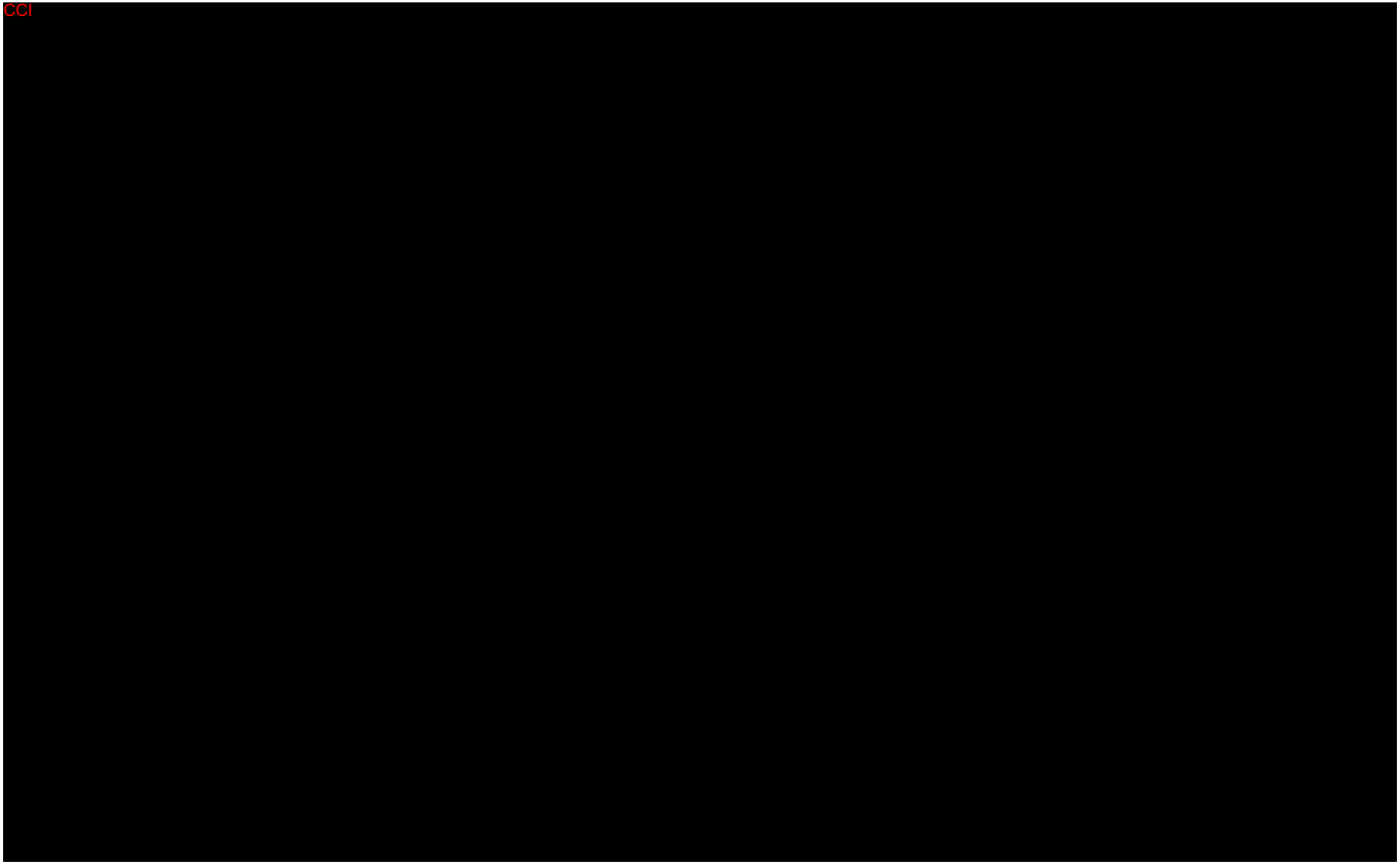

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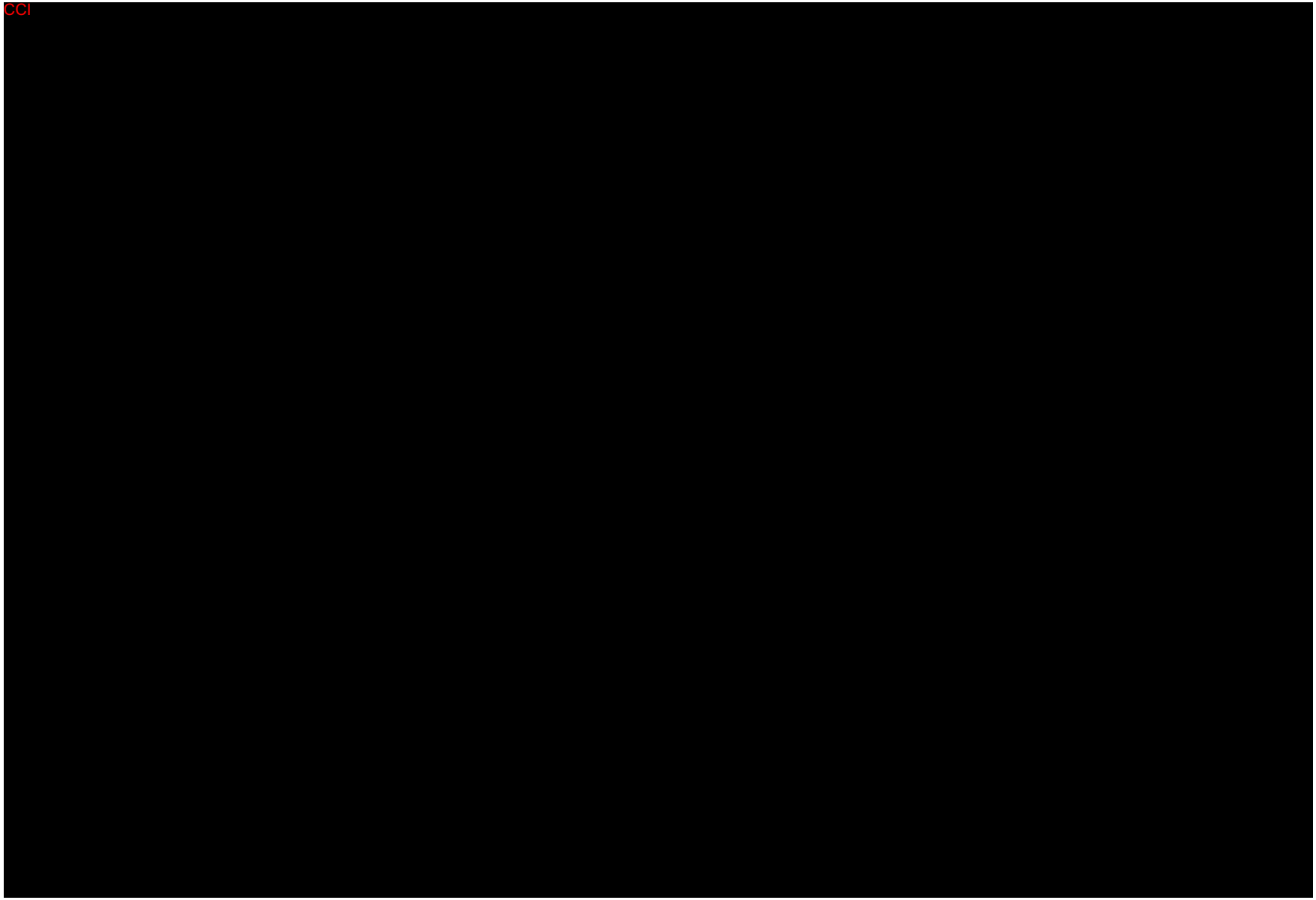

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2 INTRODUCTION

This is a Phase 2 open-label, signal finding and cohort expansion study to evaluate the safety and efficacy of MK-7684A in participants with relapsed or refractory cHL or PMBCL, FL, DLBCL, MM, and NHL.

MK-7684A is a coformulation of vibostolimab (MK-7684) and pembrolizumab (MK-3475). MK-7684 is a humanized, antagonist IgG1 mAb that binds to the immune checkpoint receptor, TIGIT expressed on T-cells and NK cells, and blocks the interaction between TIGIT and its ligands. Preclinical data has showed that anti-mTIGIT antibodies on the mIgG2a backbone (with high affinity FcγR binding) are more efficacious than anti-mTIGIT antibodies on the IgG1 D265A backbone (without FcγR binding) as single agents and in combination with mDX400 (anti-mPD-1 antibody) in multiple preclinical tumor models. Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Therefore, a strong rationale exists to develop anti-PD-1 and anti-TIGIT combination therapies. The single coformulation vial of MK-7684A will allow simplified preparation and reduced infusion times compared with separate formulations of vibostolimab and pembrolizumab administered sequentially. Effective antitumor immunity depends on presentation of a tumor antigen, activation of protective T-cell responses, and the ability to overcome tumor-based blockade of antitumor responses.

2.1 Study Rationale

Effective antitumor immunity depends on presentation of a tumor antigen, activation of protective T-cell responses, and the ability to overcome tumor-based blockade of antitumor responses. Immune checkpoint inhibitor blockade aims to reverse the immunosuppressive strategies implemented by tumors to avoid immune detection.

Enhancing the proven anti-PD-1 immune stimulatory mechanism with the T-cell stimulatory/inhibitory network TIGIT (PVRIG/TACTILE)-CD226 (DNAM1) pathway is an interesting scientific concept. TIGIT is highly coexpressed with PD-1 on both CD4+ and CD8+ T-cells during chronic inflammatory states, including viral infections and cancer [Chauvin, J. M., et al 2015] [Johnston, R. J., et al 2014]. Enhanced antitumor efficacy is observed in preclinical models when an anti-TIGIT antibody is used with an anti-PD-1 antibody. In vitro PD-1 blockade causes up-regulation of TIGIT in tumor antigen-specific CD8+ T-cells, a potential mechanism of resistance. Dual blockade of TIGIT and PD-1 increased IFN-γ, TNF, and T-cell proliferation [Chauvin, J. M., et al 2015a].

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2.1.2 Rationale for Use in Hematological Malignancies

As defined by the eligibility criteria, the following hematological malignancies were selected because each represents a significant unmet medical need despite recent advances in treatment options. In selected hematological malignancies, preliminary efficacy with PD-1 inhibitor (as summarized in [Table 7]), coexpression of TIGIT and PD-1 on T-cells and NK cells, and preliminary efficacy data with anti-TIGIT antibody and anti-PD-1 antibody in preclinical setting were observed in published data, providing rationale to evaluate such combination in selected hematological malignancies.

Classic Hodgkin's Lymphoma and Primary Mediastinal Large B-cell Lymphoma

Pembrolizumab as monotherapy has shown efficacy in adult patients with relapsed or refractory cHL in KEYNOTE-204 (median PFS 13.2 months, [95% CI: 10.9, 19.4]; ORR 66%, [95% CI: 57, 73; CR 24.5%) and KEYNOTE-87 (ORR 71%, [95% CI: 64, 77; CR

27.6%). As one of the tumor types that is sensitive to PD-1 inhibition, coexpression of TIGIT and PD-1 were also found in cHL, including CD8+ cytotoxic T-cells, CD4+ helper T-cells and FOXP3+ regulatory T-cells [Li, W., et al 2018].

Gene expression profiling has revealed that the pattern of gene expression in PMBCL is more similar to cHL than DLBCL [Rosenwald, A., et al 2003] [Savage, K. J., et al 2003], and hence these participants are included in the same cohort as cHL. Pembrolizumab as monotherapy has shown efficacy in adult and pediatric participants with relapsed or refractory PMBCL in KEYNOTE-170 (ORR 45%, [95% CI: 32, 60]; CR 18.9%).

Diffuse Large B-cell Lymphoma

Coexpression of TIGIT and PD-1 in intratumoral CD3+ T-cells was observed in DLBCL patient samples [Josefsson, S. E., et al 2019]. Previously published data with nivolumab relapsed/refractory DLBCL showed an ORR of 10%, with a median PFS of 1.9 months [Ansell, S. M., et al 2019]. Unpublished internal data from KEYNOTE-013 had 41 participants with relapsed or refractory DLBCL, of whom 5 showed remission. Retrospective analysis on DLBCL responders indicated several of them to be EBV+ or T-cell histiocyte-rich subtypes. Although sample size was small, PD-1 inhibitor showed preliminary efficacy in this aggressive type of NHL.

Follicular Lymphoma

TIGIT has been identified as an important coinhibitory receptor on T-cells in FL patients, coexpressed with PD-1 on CD8+ T-cells. TIGIT expression was associated with T-cell dysfunction, which was reversible by removing its ligand via in vitro culture [Josefsson, S. E., et al 2018]. Data, presented at the Annual American Society of Hematology meeting in 2017, from an investigator-initiated study with pembrolizumab monotherapy in relapsed or refractory indolent NHL (18 participants with FL) [Ding, W., et al 2017], reported that 2 of 18 participants with FL (11%) experienced a PR with therapy ongoing at time of data cutoff. Unpublished internal data from KEYNOTE-013 is generally consistent with these findings; 2 of 23 (9%) participants with relapsed or refractory FL showed a remission.

Non-Hodgkin's Lymphoma

Besides DLBCL, FL and PMBCL, other types of NHL originating from B lymphocytes will also be evaluated in this study, which may include MCL, MZL. Although anti-PD-1 monotherapy data in the other types of NHL remains incomplete, there is molecular evidence that TIGIT and PD-1 are likely to inhibit T-cell antitumor activity through interaction with tumor cells and/or endothelial cells expressing the ligands in MCL and MZL [Josefsson, S. E., et al 2019].

Multiple Myeloma

Similar to solid tumors, immune effector cells from MM patients are efficiently primed but become dysfunctional in several aspects like cytokine secretion defects, proliferative arrest, and expression of multiple coinhibitory receptors, including TIGIT and PD-1. Through assessing cytokine release by BM cells from patients with MM on stimulation, TIGIT

expression has been associated with a subset of exhausted CD8+ T-cells with severely impaired effector function [Guillerey, C., et al 2018] [Lozano, E., et al 2020]. In preclinical setting, MM progression is associated with high levels of TIGIT expression on CD8+ T-cells and impaired effector functions. CD8+ T-cells from the BM of MM-relapsed mice showed increased expression of TIGIT, PD-1, LAG-3 and TIM-3. In addition, anti-TIGIT mAbs treatment significantly reduced tumor burden and prolonged the survival in CD8+ T-cell-dependent manner [Guillerey, C., et al 2018]. Lozano et al showed that TIGIT blockage depleted FoxP3+ Tregs while increasing proliferation of IFN-□-producing CD4+ T-cell from patients with multiple myeloma via in vitro experiment [Lozano, E., et al 2020]. These molecular and preclinical data provided scientific rationale in targeting both TIGIT and PD-1 pathways in this disease.

Treatment effect with anti-PD-1 monotherapy in MM showed some preliminary efficacy with safety profile consistent with other cancers. A study with PD-1 monotherapy reported 1 patient experienced a response to nivolumab among 27 MM participants and achieved CR after radiotherapy [Lesokhin, A. M., et al 2016]. In KEYNOTE-013 study, the best response among 30 relapsed or refractory MM participants was SD (DCR: 56.7%), and 2 participants had unconfirmed responses per laboratory assessment. Pembrolizumab was generally well tolerated in these participants after a median follow-up of 19.9 months. Most treatment-related AE's after pembrolizumab monotherapy were mild to moderate[Ribrag, V., et al 2019].

In summary, the safety profile observed with anti-PD-1 monotherapy in MM patients, safety profile of vibostolimab and pembrolizumab combination in patients' solid tumors (vibostolimab/MK-7684A IB), molecular evidence of TIGIT's role in MM patients and preclinical data with anti-TIGIT mAbs support the rationale to evaluate this coformulation of vibostolimab and pembrolizumab in relapsed or refractory MM.

Efficacy with PD-1 monotherapy in selected B-cell malignancies and multiple myeloma is summarized in Table 7 below. These data provided context for assessing this coformulation, vibostolimab and pembrolizumab, in these hematological malignancies.

Table 7 Efficacy Results With PD-1 Antibody as Monotherapy in Selected B-cell Malignancies and Multiple Myeloma

Disease Type	No. of Participants	ORR	CR	Median PFS (months)	Median OS (months)	Study Treatment	References
r/r cHL	151	66%	25%	13.2	-	Pembrolizumab monotherapy	Pembrolizumab USPI, KEYNOTE-204 [U.S. Prescribing Information 2020]
r/r PMBCL	53	45%	11%	-	-	Pembrolizumab monotherapy	Pembrolizumab USPI, KEYNOTE-170 [U.S. Prescribing Information 2020]
r/r DLBCL	87	10%	-	1.9	12.2	Nivolumab monotherapy	[Ansell, S. M., et al 2019] (Failed ASCT in Checkmate 139)
r/r FL	18	11%	-	-	-	Pembrolizumab monotherapy	[Ding, W., et al 2017]
r/r MM	30	0a	0	2.7	20.2	Pembrolizumab monotherapy	[Ribrag, V., et al 2019]

Abbreviations: ASCT=autologous stem cell transplant; cHL=classic Hodgkin's Lymphoma; CR=complete response; DLBCL=Diffuse Large B-cell Lymphoma; FL=Follicular Lymphoma; MM=Multiple Myeloma; No.=number; ORR=objective response rate; OS=overall survival; PFS=Progression-free survival; PMBCL=Primary Mediastinal Large B-cell Lymphoma; r/r=relapsed/refractory; USPI=United States Prescribing Information.

-: not reported

a: Two unconfirmed responses based on laboratory assessment. Response not confirmed because participants started subsequent anticancer therapy.

A more comprehensive review of nonclinical and clinical data is included in the MK-7684 IB.

2.2 Background

2.2.1 Selected Hematological Malignancies

Hodgkin's lymphoma accounts for approximately 11% of all lymphomas in western countries [Landgren, O. 2007], with an incidence of 2.3/100,000 and account for approximately 0.4/100,000 of all cancer deaths [Eichenauer, D. A., et al 2014]. Classical HL is divided into 4 histologic subtypes: nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted [Landgren, O. 2007].

Non-Hodgkin's lymphomas are a heterogeneous group of lymphoproliferative disorders originated in B lymphocytes, T lymphocytes, or NK cells. Non-Hodgkin's lymphomas is the fifth leading site of new cancer cases among men and women, accounting for 4% to 5% of new cancer cases and 3% of cancer-related deaths [National Comprehensive Cancer Network, Inc. 2008].

DLBCL is the most common type of adult NHL in both North America and Europe, making up 31% of NHL [National Comprehensive Cancer Network, Inc. 2008]. Patients with double-hit lymphomas (rearrangement of BCL2 and/or BCL6 and MYC genes) have a poor prognosis compared with patients without. Four-year OS rate was 25% versus 61% in a retrospective review of 117 patients with relapsed or refractory double-hit lymphomas compared with DLBCL who underwent autologous SCT [Herrera, A. F., et al 2017].

FL is the second most common NHL, comprising 17% to 22% of cases. FL is incurable in most patients, and relapse generally occurs with poor outcomes after early relapse or chemoimmunotherapy-resistant disease [Gopal, A. K., et al 2018]. Some patients with relapse and resistant disease after standard therapies may have poor outcomes (2-year OS rate of 38% in POD24 study) [Freeman, C. L., et al 2019]. Data suggests that the tumor microenvironment may contribute to the development and progression of FL, and the interaction of FL cells with immune cells in the tumor may influence the clinical course and response to therapy [Gopal, A. K., et al 2018].

PMBCL is a distinct subtype of NHL that accounts for 2% to 4% of all cases [Steidl, C. 2011]. PMBCL was considered a subtype of DLBCL; however, the WHO classification listed PMBCL as a separate entity. PMBCL patients treated with multiagent chemotherapy appear to have a better survival compared with DLBCL [Steidl, C. 2011].

Besides DLBCL, FL, and PMBCL, other types of NHL originating from B lymphocytes will also be evaluated in this study, which may include MCL and MZL. Refer to eligibility criteria for detail.

Multiple myeloma is a malignant monoclonal plasma cell disorder that is characterized by end-organ damage, such as CRAB (calcium [elevated], renal failure, anemia, bone lesions) [Mahindra, A., et al 2012] [Palumbo, A., et al 2014]. Multiple myeloma accounts for 10% of all hematological malignancies and has an age-adjusted incidence of approximately 4 per 100,000 [Mahindra, A., et al 2012]. The combination strategy of anti-PD-1 with standard therapy, IMiD was explored in MM; pembrolizumab in combination with pomalidomide or lenalidomide with dexamethasone. The combination failed to improve clinical outcomes compared with standard therapy alone for participants with relapsed/refractory multiple myeloma (KEYNOTE-183, pomalidomide as part of standard therapy) [Mateos, M. V., et al 2019] and treatment-naïve multiple myeloma (KEYNOTE 185, lenalidomide as part of standard therapy) [Usmani, S. Z., et al 2019]. Data from an unplanned interim analyzes showed an imbalance in number of deaths between treatment groups. However, the interim analyses were underpowered and inconclusive because of the shortened follow-up at study termination. Median follow-up was 8.1 months in KEYNOTE 183 and 6.6 months in KEYNOTE 185. In addition, disease characteristics were generally not balanced between treatment groups at the time of early study termination. Specifically, a greater proportion of

those in the pembrolizumab plus standard therapy group than in the standard therapy group had risk factors associated with poorer prognosis. This imbalance might account for the difference in early death observed that led to early termination of KEYNOTE-183 and KEYNOTE 185.

2.2.2 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between TILs in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. TILs can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

2.2.2.1 Vibostolimab Background

Vibostolimab is a humanized, antagonist mAb that binds to the immune checkpoint receptor, TIGIT, and blocks the interaction between TIGIT and its ligands. This human IgG1 antibody is being developed as a cancer immunotherapeutic with the potential to be used as monotherapy or to be combined with pembrolizumab (a humanized anti-PD-1 receptor antibody) to increase benefit to patients with various tumor types.

TIGIT is an immunomodulatory receptor expressed primarily on activated CD4+ and CD8+ T-cells, NK cells, and NKT cells. TIGIT is one of multiple immune checkpoint molecules that maintain immune homeostasis and prevent uncontrolled immune activation. Its structure reveals a single extracellular immunoglobulin domain, a transmembrane region, an immunoglobulin tail tyrosine-like phosphorylation motif, and an immunoreceptor tyrosine-based inhibitory motif.

TIGIT forms part of a costimulatory network that consists of a positive (CD226) and negative (TIGIT) immunomodulatory receptor on T-cells, and ligands (CD155 and CD112) expressed on tumor cells and antigen presenting cells [Levin, S. D., et al 2011]. Whereas CD226 is widely expressed on most immune cells, TIGIT is highly expressed on memory T-cells, T regs, NK cells, and NKT cells [Dardalhon, V., et al 2005] [Stanietsky, N., et al 2009]. CD155/PVR (poliovirus receptor) and CD112/PVRL-2 are 2 nectin family members that are widely expressed, both on cells of the hematopoietic system and on fibroblasts and endothelial cells. Functionally, these receptor ligands are involved in cell adhesion and motility. CD155 is reported to be overexpressed in several tumor types and has been found to be induced by Ras activation and genotoxic stress [Carlsten, M., et al 2007] [Hirota, T., et al 2005] [Soriani, A., et al 2009] [Stanietsky, N., et al 2009].

In addition, TIGIT is highly coexpressed with PD-1 on both CD4+ and CD8+ TILs including T regs, in mouse and human tumors, and has been reported to be coexpressed with PD-1 and TIM-3 on the TILs with the most exhausted phenotype [Chauvin, J. M., et al 2015]

[Johnston, R. J., et al 2014]. Furthermore, enhanced antitumor efficacy is observed in preclinical models when an anti-TIGIT antibody is used with an anti-PD-1 antibody. We hypothesize, therefore, that combining vibostolimab with pembrolizumab will offer substantially augmented antitumor efficacy.

2.2.2.2 Pembrolizumab Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD 1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB.

2.2.3 Preclinical and Clinical Studies

2.2.3.1 CCI

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2.2.3.2 Pembrolizumab Preclinical and Clinical Studies

Refer to the IB for preclinical and clinical study data for pembrolizumab.

2.2.4 Ongoing Clinical Studies

Refer to the IBs for detailed background information on vibostolimab/MK-7684A and pembrolizumab.

2.2.4.1 Pembrolizumab Ongoing Clinical Trials

Numerous interventional clinical studies involving pembrolizumab are currently ongoing in a number of advanced solid tumor indications, as well as in hematological malignancies.

Additional details regarding other ongoing studies of pembrolizumab in hematological malignancies may be found in the IB.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

The existing data in available studies suggest that blockade of TIGIT with vibostolimab offers a new immunological mechanism, which has been shown to enhance the activity of pembrolizumab in preclinical and early clinical observations. Furthermore, since this pathway is independent of PD-L1 expression, it may offer a particular benefit to all patients, regardless of PD-L1 status. Inhibiting TIGIT in combination with PD-1 blockade is a therapeutic strategy being investigated for the first time in patients with a variety of hematologic malignancies with limited treatment options, and the benefit/risk assessment for patients in this study may be favorable.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Formal hypothesis testing will not be performed in this protocol. In male and female participants who are 18 years of age or older with various relapsed/refractory hematological malignancies.

Tertiary/exploratory endpoints will not be collected after the end of the study.

Primary Objective	**Primary Endpoint**
Part 1: To determine the safety and tolerability of MK-7684A (Cohorts A to F)	Dose-Limiting Toxicities Adverse events Discontinuation of study intervention due to an AE
Secondary Objectives	**Secondary Endpoints**
Part 1: To evaluate ORR following administration of MK-7684A (Cohorts A to F) per disease-specific criteria as assessed by the investigator.	Objective response: CR or PR (for MM includes stringent CR, CR, and VGPR, PR)
Part 1: To evaluate the DOR following administration of MK-7684A (Cohorts A to F)	DOR, defined as the time from first documented evidence of CR or PR (for MM includes stringent CR, CR, and VGPR, PR) until disease progression per disease-specific criteria as assessed by the investigator or death due to any cause, whichever occurs first.
Part 1: To evaluate the DCR following administration of MK-7684A (Cohorts A to F)	DCR: CR, PR or SD (for MM, also including stringent CR, VGPR, MR) for at least 12 weeks prior to any evidence of progression.
Part 1: To characterize the PK profile of vibostolimab (Cohorts A to F)	Trough concentration (C_{trough}) Maximum concentration (C_{max})

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4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, open-label, nonrandomized study to evaluate the safety and efficacy of MK-7684A (a coformulation of vibostolimab and pembrolizumab) and vibostolimab monotherapy in participants with various hematological malignancies.

The study will be divided into 2 parts: signal finding (Part 1) and cohort expansion (Part 2). Overall, 330 participants may be enrolled into both parts of the study; Part 1 will include approximately 180 participants with relapsed/refractory disease in Cohorts A to F to be administered MK-7684A Q3W for up to 35 cycles; Part 2 may include approximately 120 participants with relapsed/refractory disease in Cohorts B to E to be administered MK-7684A Q3W and approximately 30 participants in Cohort G to be administered vibostolimab monotherapy Q3W for up to 35 cycles. The decision to open expansion cohorts in Part 2 will depend on the benefit and risk profile observed in Part 1 and Sponsor's development strategy.

AEs will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE Version 5.0. Each participant will be monitored for AEs and SAEs for 30 days and 90 days, respectively, after discontinuation of study intervention.

After documenting the informed consent, suitable candidates will be screened to assess whether they meet all study eligibility criteria. Eligible participants will be assigned to 1 of 6 cohorts in Part 1 (Cohorts A to F) according to their hematologic malignancy and prior therapy received. All participants will be dosed with MK-7684A. No dose titration is currently being planned in Part 1. For Part 2, eligible participants will be alternately assigned to Cohorts B to E, according to their hematologic malignancy, to receive MK-7684A or Cohort G, to receive vibostolimab monotherapy. The study will be conducted in conformance with GCP.

After approval of Amendment 5, participants will not be offered second course treatment. The study will end 90 days after the last participant completes 35 cycles of treatment or terminates early, whichever comes first and second course option for treatment is no longer available. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study and no further imaging or participant contacts will be required.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.1.1 Signal Finding (Part 1)

Approximately 180 participants may be enrolled in 1 of the 6 disease-specific cohorts (approximately 30 participants per cohort) in Part 1 of the study. The cohorts will include:

- Cohort A: Participants with cHL or PMBCL who are relapsed or refractory to at least 1 line of prior therapy (cHL) or at least 2 lines of prior therapies (PMBCL). Prior therapy must not include an anti-PD-1/L1 treatment.
- Cohort B: Participants with cHL or PMBCL who are relapsed or refractory to at least 2 lines of prior therapies (cHL) or at least 3 lines of prior therapies (PMBCL). These prior therapies must include a prior anti-PD-1/L1 treatment.
- Cohort C: Participants with FL who are relapsed or refractory to at least 2 lines of prior therapy.
- Cohort D: Participants with DLBCL who are relapsed or refractory to at least 2 lines of prior therapy.
- Cohort E: Participants with MM who are relapsed or refractory to at least 3 lines of prior therapy and have exhausted all approved lines of therapy.
- Cohort F: Participants with NHL who are relapsed or refractory to at least 2 lines of prior therapy.

Further details regarding prior treatment, including SCT requirements, are described in Section 5.1 per cohort.

The primary endpoints of Part 1 of the study are DLTs, AEs, and AEs resulting in treatment discontinuation with the aim to move to cohort expansion to determine effectiveness. The definition of DLTs is provided in Section 4.3.4.

In Part 1, safety data from the first 12 participants (from any cohort) treated with MK-7684A and deemed as DLT evaluable (see definition in Section 9.5.2 and replacement requirements in Section 5.5.1) will be reviewed to determine tolerability of MK-7684A. DLT observation period is defined as the first 2 cycles (first 6 weeks) of study treatment without discontinuation. DLTs will be monitored in the first 12 DLT evaluable participants on an ongoing basis, based on timely data entry and close communication between investigator sites and Sponsor's study team. The Sponsor will formally evaluate the DLT rate when at least 12 DLT evaluable participants have completed the DLT observation period to confirm the safety of MK-7684A. If 4 or fewer participants have a DLT (DLT rate of ≤33.3%), the coformulation will be considered tolerable. If 5 or more of the first 12 participants have a DLT (DLT rate of ≥41.7%), enrollment will be paused to evaluate all available data and to determine whether or not to stop enrollment into Part 1 of the study due to unacceptable toxicity.

After the initial DLT review for the first 12 evaluable participants (from any cohort), all safety data will be reviewed every 6 months, thereafter, for all of the participants as described in Section 9.7.1. Enrollment will not be halted unless a potential safety signal

arises during the conduct of the study. Considerations may include, but not limited to, the number of DLT's, the clinical course of the toxicities, and benefit/risk assessment in conjunction with treating physicians.

For Cohort B participants (relapsed or refractory cHL or PMBCL who have been previously treated with a PD-1/L1 inhibitor), pretrial scans are required to be reviewed by ICR to verify disease progression on prior therapy. If disease progression cannot be verified, additional participants may be enrolled to ensure approximately 30 eligible participants are enrolled.

One futility assessment is planned for each cohort, when the first 12 participants per cohort in Part 1 have completed at least 1 postbaseline efficacy assessment. Further details are provided in Section 9.7.2.

All participants who achieve a SD, PR, or CR may be eligible for up to an additional 17 cycles of MK-7684A if there is an investigator-determined disease progression as per disease-specific criteria after initial treatment or first course has been completed or stopped for confirmed CR, PR, or SD. Further details are provided in Section 6.1.2 and Section 1.3.3.

4.1.2 Cohort Expansion (Part 2)

The decision to open expansion cohorts in Part 2 will depend on an interim review of Part 1 data per cohort of approximately 30 participants to evaluate the benefit/risk of MK-7684A in each disease type. If a favorable profile is observed in any particular disease type, Part 2 cohorts may be initiated.

Approximately 150 participants may be enrolled in 1 of the 5 cohorts (approximately 30 participants per cohort) in Part 2 of the study. Participants enrolled in Cohorts B to E (PD-1/L1 refractory, relapsed or refractory cHL or PMBCL; relapsed or refractory FL; relapsed or refractory DLBCL; and relapsed or refractory MM) will be treated with MK-7684A and those enrolled in Cohort G (PD-1/L1 refractory, relapsed or refractory cHL or PMBCL; relapsed or refractory FL; relapsed or refractory DLBCL; and relapsed or refractory MM) will be treated with vibostolimab monotherapy. Cohort allocation for Part 2 will be alternating with 1 participant for each disease type being enrolled into Cohort G first and the second into Cohort B to E, whichever is applicable. The cohorts will include:

- Cohort B: Participants with cHL or PMBCL who are relapsed or refractory to at least 2 lines of prior therapies (cHL) or at least 3 lines of prior therapies (PMBCL). These prior therapies must include an anti-PD-1/L1 treatment.
- Cohort C: Participants with FL who are relapsed or refractory to at least 2 lines of prior therapy.
- Cohort D: Participants with DLBCL who are relapsed or refractory to at least 2 lines of prior therapy.
- Cohort E: Participants with MM who are relapsed or refractory to at least 3 lines of prior therapy and have exhausted all approved lines of therapy.

- Cohort G: The following hematological malignancies, with an initial limit of 7 participants per disease type, will be included. Enrollment may be adjusted depending on opening of disease-specific cohort(s) in Part 2:
  - Participants with cHL or PMBCL who are relapsed or refractory to at least 2 line of prior therapy (cHL) or at least 3 lines of prior therapies (PMBCL). These prior therapies must include an anti-PD-1/L1 treatment,
  - Participants with FL who are relapsed or refractory to at least 2 lines of prior therapy,
  - Participants with DLBCL who are relapsed or refractory to at least 2 lines of prior therapy, AND
  - Participants with MM who are relapsed or refractory to at least 3 lines of prior therapy and have exhausted all approved lines of therapy.

Further details regarding prior treatment, including SCT requirements, are described in Section 5.1 per cohort.

4.2 Scientific Rationale for Study Design

This Phase 2, nonrandomized, open-label, signal finding and cohort expansion study will first establish the safety and tolerability of MK-7684A, and second, provide proof of concept in various relapsed or refractory hematological malignancies. The hematologic malignancies selected for this study are those disease types known to represent a significant unmet medical need as well as the expression of TIGIT and responses to anti-PD-1/L1 monotherapy, as summarized in Section 2.2.1.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Endpoint definitions are provided in Section 9.4.

After the approval of Amendment 5, the study will end 90 days after the last participant completes 35 cycles of treatment or terminates early, whichever comes first, and second course option for treatment is no longer available. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study, and no further imaging or participant contacts will be required.

Objective Response Rate

ORR is a secondary efficacy endpoint for Part 1 of the study.

Treatment effect measured by ORR can represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, number of CRs, durability of response, disease setting, location of the tumors, available therapy, and risk-benefit relationship.

Each hematological malignancy has specific response criteria developed by experts that will be applied in the assessment of ORR (for Cohorts A to F) as summarized in Appendix 8.

Duration of Response

DOR is a secondary efficacy endpoint for Part 1 of the study.

Improved DOR can result in a meaningful delay in disease progression as opposed to a temporary response without lasting benefit.

Disease Control Rate

DCR is a secondary efficacy endpoint for Part 1 of the study.

This includes participants who have achieved tumor response per relevant response criteria or have showed SD for at least 12 weeks before any evidence of progression. The proportion of participants with tumor response or SD can result in a meaningful delay in disease progression.

Progression-free Survival

PFS is an exploratory efficacy endpoint for Part 1 of the study.

PFS is a surrogate endpoint that reflects tumor growth and includes deaths and therefore correlates to OS.

Overall Survival

OS is an exploratory efficacy endpoint for Part 1 of the study.

OS is a precise and reliable measure of survival, a key clinical endpoint.

Minimal Residual Disease

MRD is an exploratory efficacy endpoint for participants with MM in Cohort E for Part 1.

MRD negativity is a surrogate endpoint that correlates with improved OS and PFS.

4.2.1.2 Safety Endpoints

The safety and tolerability of MK-7684A will be assessed by clinical evaluation of AEs and inspection of other study parameters including vital signs, physical examination, and laboratory safety tests at time points specified in the SoA. AEs will be assessed as defined by CTCAE, Version 5.0 and recorded according to Section 8.4 and Appendix 3. In addition, DLTs will be used to determine the safety and tolerability of MK-7684A. The definition of a DLT is provided in Section 4.3.4.

4.2.1.3 CCI

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CCI [redacted]

4.2.1.3.1 CCI [redacted]

CCI [redacted]

4.2.1.3.2 CCI [redacted]

CCI [redacted]

4.2.1.4 CCI [redacted]

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4.2.1.5 CCI [redacted]

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CCI [redacted]

4.2.1.6 CCI [redacted]

CCI [redacted]

4.2.1.7 CCI [redacted]

CCI [redacted]

4.3 CCI [redacted]

4.3.1 CCI [redacted]

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4.3.2

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[redacted]

4.3.5 Maximum Dose Exposure for This Study

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

Recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

Early study termination will be the result of the criteria specified below:

1. Incidence or severity of adverse drug reactions in this or other studies suggest a potential health hazard to participants

2. Plans to modify or discontinue the development of the study medication

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-7684A.

5 STUDY POPULATION

Male/female participants at least 18 years of age with relapsed or refractory hematological malignancies will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

Participants are required to have a confirmed diagnosis of:

1. Cohort A: relapsed or refractory cHL or PMBCL, not previously treated with an anti-PD-1/L1 therapy

cHL

a) Diagnosis of cHL, according to the WHO classification of neoplasms of the hematopoietic and lymphoid tissues [Swerdlow, S. H., et al 2016].
b) Have relapsed*a or refractory*b cHL to at least 1 prior line of therapy and:
   i. Have failed to achieve a response or progressed after auto-SCT, OR
   ii. Were unable to achieve a CR or PR to salvage chemotherapy, and therefore did not proceed to auto-SCT, or were ineligible for auto-SCT due to age/comorbidities as judged by the treating physician.

   *a Relapsed Disease: Progression of disease after achieving a remission to the most recent therapy

   *b Refractory Disease: Failure to achieve CR or PR to the most recent therapy

   Note: A planned treatment approach of induction therapy followed by auto-SCT, followed by maintenance, is considered 1 line of therapy
c) Have not been previously treated with an anti-PD-1/L1 therapy.
   Note: Refer to Appendix 7 for Italy-specific requirements related to Cohort A.

   Note: Refer to Appendix 7 for France-specific requirements related to Cohort A.

PMBCL

d) Diagnosis of PMBCL, according to the WHO classification of neoplasms of the hematopoietic and lymphoid tissues [Swerdlow, S. H., et al 2016].

e) Have relapsed*a or refractory*b PMBCL to at least 2 prior lines of therapies and:

i. Have failed to achieve a response or progressed after auto-SCT, OR

ii. Were unable to achieve a CR or PR to salvage chemotherapy, and therefore did not proceed to auto-SCT, or are ineligible for auto-SCT due to age/comorbidities as judged by the treating physician.

*a Relapsed Disease: Progression of disease after achieving a remission to the most recent therapy. *b Refractory Disease: Failure to achieve CR or PR to the most recent therapy.

Note: A planned treatment approach of induction therapy followed by auto-SCT, followed by maintenance, is considered 1 line of therapy.

f) Participants must be relapsed or refractory to CAR-T-cell therapy or unable to receive it.

g) Must have received rituximab as part of prior treatment.

h) Have not been previously treated with an anti-PD-1/L1 therapy.

2. Cohort B: relapsed or refractory cHL or PMBCL previously treated with an anti-PD-1/L1 therapy

cHL

a) Diagnosis of cHL, according to the WHO classification of neoplasms of the hematopoietic and lymphoid tissues [Swerdlow, S. H., et al 2016].

b) Have relapsed*a or refractory*b cHL to at least 2 prior lines of therapies (including prior PD-1/L1 therapy) and:

i. Have failed to achieve a response or progressed after auto-SCT, OR

ii. Were unable to achieve a CR or PR to salvage chemotherapy, and therefore did not proceed to auto-SCT, or were ineligible for auto-SCT due to age/comorbidities as judged by the treating physician.

*a Relapsed Disease: Progression of disease after achieving a remission to the most recent therapy.

*b Refractory Disease: Failure to achieve CR or PR to the most recent therapy.

Note: A planned treatment approach of induction therapy followed by autologous SCT, followed by maintenance, is considered 1 line of therapy.

c) Have progressed on-treatment with an anti-PD-1/L1 mAb administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies. Anti-PD-1/L1 treatment progression is defined by meeting all of the following criteria:

i. Have received at least 2 doses of an anti-PD-1/L1 mAb that has been approved in cHL and administered at the approved dose and schedule.

ii. Have showed disease progression after an anti-PD-1/L1 mAb as defined by Lymphoma Disease Response criteria (Cheson or Lugano). This determination is made by the investigator.

i. Progressive disease has been documented within 12 weeks from the last dose of an anti-PD-1/L1 mAb or during therapy.

ii. Note: Intervening therapies are allowed in between last anti-PD-1/L1 dose and enrollment on-study if all other criteria are met.

iii. Have submitted pretrial imaging.

Note: The investigator site's study team must have reviewed pretrial images that are of diagnostic quality from at least 2 dates (before treatment with anti-PD-1/L1 inhibitor and then on or after therapy) to determine that radiographic progression has occurred per Lymphoma Disease Response criteria (Cheson or Lugano) after initiation of a PD-1/L1 inhibitor. Verification of progression by ICR will not be required before enrollment in the study; however, basic image quality review will be performed to ensure images are readable for potential ICR.

Note: Refer to Appendix 7 for France- and Germany-specific requirements related to Cohort B.

PMBCL

d) Diagnosis of PMBCL, according to the WHO classification of neoplasms of the hematopoietic and lymphoid tissues [Swerdlow, S. H., et al 2016].

e) Have relapsed*[a] or refractory*[b] PMBCL to at least 3 prior lines of therapies (including prior PD-1/L1 therapy) and:

i. Have failed to achieve a response or progressed after auto-SCT, OR

ii. Were unable to achieve a CR or PR to salvage chemotherapy, and therefore did not proceed to auto-SCT, or are ineligible for auto-SCT due to age/comorbidities as judged by the treating physician.

*a Relapsed Disease: Progression of disease after achieving a remission to the most recent therapy.

*b Refractory Disease: Failure to achieve CR or PR to the most recent therapy.

Note: A planned treatment approach of induction therapy followed by auto-SCT, followed by maintenance, is considered 1 line of therapy.

f) Must have previously received rituximab as part of prior treatment.

g) Participants must be relapsed or refractory to CAR-T-cell therapy or unable to receive it.

h) Have progressed on-treatment with an anti-PD-1/L1 mAb administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies. Anti-PD-1/L1 treatment progression is defined by meeting all of the following criteria:

i. Have received at least 2 doses of an anti-PD-1/L1 for PMBCL treatment, and

ii. Have showed disease progression after an anti-PD-1/L1 mAb as defined by Lymphoma Disease Response criteria (Cheson or Lugano). This determination is made by the investigator, and

iii. Progressive disease has been documented within 12 weeks from the last dose of an anti-PD-1/L1 mAb or during therapy, and

Note: Intervening therapies are allowed in between last anti-PD-1/L1 dose and enrollment on-study if all other criteria are met.

iv. Have submitted pretrial imaging.

Note: The investigator site's study team must have reviewed pretrial images that are of diagnostic quality from at least 2 dates (before treatment with anti-PD-1/L1 inhibitor and then on or after therapy) to determine that radiographic progression has occurred per Lymphoma Disease Response criteria (Cheson or Lugano) after initiation of a PD-1/L1 inhibitor. Verification by ICR of progression will not be required before enrollment in the study; however, basic image quality review will be performed to ensure images are readable for potential ICR.

Note: Refer to Appendix 7 for France-specific requirements related to Cohort B.

3. Cohort C: relapsed or refractory FL
   1. Diagnosis of FL (all grades permitted; 1 to 3b), according to the WHO classification of neoplasms of the hematopoietic and lymphoid tissues [Swerdlow, S. H., et al 2016].
   2. Participants who are relapsed or refractory to at least 2 prior lines of therapy, chemoimmunotherapy and immunomodulatory agents (ie, lenalidomide + rituximab). Participants must have received and failed, been intolerant to, or determined by their treating physician to be a poor candidate or ineligible for a PI3K inhibitor per local (institution) guidelines. Participants who are ineligible for standard treatment or who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of that treatment and precluding retreatment with the same agent before progression of disease will also be eligible.

      Note: A planned treatment approach of induction therapy followed by auto-SCT, followed by maintenance, is considered 1 line of therapy.

      Participants must be relapsed or refractory to CAR-T-cell therapy or unable to receive it.

4. Cohort D: relapsed or refractory DLBCL
   a) Diagnosis of DLBCL, according to the WHO classification of neoplasms of the hematopoietic and lymphoid tissues [Swerdlow, S. H., et al 2016]. Cell of Origin is known for DLBCL, NOS, germinal center B-cell type or activated B-cell type. DLBCL with over-expression of MYC, BCL2, and/or BCL6 proteins without rearrangement are also classified as DLBCL.

b) Participants must have progressed after at least 2 lines of previous therapy, including progression after an auto-SCT, or are not a candidate (per institutional criteria) for an auto-SCT. Participants who are ineligible for standard treatment or who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of that treatment and precluding retreatment with the same agent before progression of disease will also be eligible.

   Note: A planned treatment approach of induction therapy followed by auto-SCT, followed by maintenance, is considered 1 line of therapy.

c) Participants must be relapsed or refractory to CAR-T-cell therapy or unable to receive it.

d) Participants must have exhausted or be ineligible for or intolerant to all treatments, which in the opinion of the investigator are standard of care for their disease.

   Note: Refer to Appendix 7 for Germany-specific requirements related to Cohort D.

5. Cohort E: relapsed or refractory MM

a) Have histologically or cytologically confirmed diagnosis of active MM as per IMWG criteria [Rajkumar, S. V., et al 2014].

b) Have measurable disease defined as meeting at least 1 of the following criteria:

c) Serum monoclonal protein (M-protein) levels ≥0.5 g/dL (≥5 g/L), OR

d) Urine monoclonal protein (M-protein) levels ≥200 mg/24 h, OR

e) For participants without measurable serum and urine M-protein levels, an abnormal serum-FLC ratio (FLC k/l <0.26 or >1.65) with involved FLC level ≥100 mg/L (normal serum FLC k/l value: 0.26-1.65).

f) Must have undergone stem cell transplant and have relapsed after auto-SCT or have failed to achieve a CR or PR following auto-SCT, or is considered ineligible for auto-SCT

g) Note: A planned treatment approach of induction therapy followed by auto-SCT, followed by maintenance, is considered one line of therapy.

h) Participants must have received all regionally approved antimyeloma therapy including IMiD (pomalidomide, lenalidomide, or thalidomide), proteasome inhibitor (bortezomib, carfilzomib, or ixazomib), steroids, anti-CD38 monoclonal antibody, selinexor, and anti-BCMA therapies alone or in combination.

i) Note: Exception in cases where an approved therapy is not available or not suitable for the participant.

j) Participants must have failed their last line of therapy, defined as 1 of the following:

   i. Refractory: Nonresponsive (ie, failure to achieve at least PR) while on primary or salvage therapy, or documented progressive disease on or within 60 days of completing treatment, OR

   ii. Relapsed: disease progression following prior response to antimyeloma therapy, participants must have relapsed within 6 months after stopping treatment.

   Note: Participants must be relapsed or refractory to CAR-T-cell therapy or unable to receive it.

6. Cohort F: relapsed or refractory NHL
   a) Have histologically confirmed diagnosis of B-cell lymphoma other than cHL, PMBCL, DLBCL (as described in inclusion criterion 4a), or FL, according to the WHO classification of neoplasms of the hematopoietic and lymphoid tissues [Swerdlow, S. H., et al 2016]. Examples include transformed indolent lymphoma, classical MCL, MZL (both nodal and extranodal), splenic MZL, lymphogranulomatosis, intravascular large B-cell lymphoma, T-cell/histiocyte-rich large cell lymphoma, high-grade B-cell lymphoma (with MYC, BCL2, and/or BCL6 rearrangements), DLBCL with chronic inflammation, B-cell lymphoma unclassifiable, EBV+ DLBCL-NOS and ALK+ large B-cell lymphoma, or small lymphocytic lymphoma. For MCL, documentation of either over-expression of cyclin D1 or presence of t(11;14) is required.
   b) Participants with MCL must have received prior Bruton's tyrosine kinase inhibitor therapy.
   c) Participants must have progressed after at least 2 lines of previous therapy. Participants must have received and failed, been intolerant to, or determined by their treating physician to be a poor candidate or ineligible for a PI3K inhibitor per local (institution) guidelines. Participants who are ineligible for standard treatment or who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of that treatment and precluding retreatment with the same agent before progression of disease will also be eligible. Participants with a indolent lymphoma are required to meet criteria for systemic therapy.

      Note: A planned treatment approach of induction therapy followed by auto-SCT, followed by maintenance, is considered 1 line of therapy.
   d) Participants must have exhausted or be ineligible for or intolerant to all standard of care treatment options for their disease per investigator's judgment before enrollment.
7. Cohorts A, B, C, D, and F (non-FDG-avid lymphoma participants):
   a) Have measurable disease, defined as at least 1 lesion that can be accurately measured in at least 2 dimensions with spiral CT scan. Minimum measurement must be >15 mm in the longest diameter or >10 mm in the short axis.

      Note: If a target lesion is selected for an excisional screening biopsy, the inclusion criterion for measurable disease must still be met after such biopsy.

   b) Be able to provide newly obtained bone marrow biopsy material for tumor response assessment by local investigator sites.
8. Cohort E (MM participants): Be able to provide newly obtained (within 3 months) bone marrow biopsy or aspirate material for disease assessment at local institution and submit sample to Sponsor-designated central laboratory for biomarker analysis. If bone marrow biopsy or aspiration was performed within 3 months before screening but participant had anticancer treatment after biopsy, the bone marrow biopsy or aspiration should be repeated.
9. Participants who have received CAR T-cell therapy before study entry and have experienced disease progression post therapy may be considered for the study.

Demographics

10. Is male or female, ≥18 years of age, at the time of providing the informed consent.

Female Participants

11. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

    - Is not a WOCBP
      OR

    - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
      - A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 72 hours for serum sample and within 24 hours for urine test before the first dose of study intervention.
      - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
      - Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.7.
      - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

12. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

13. Participants with endocrine-related conditions, including Type 1 Diabetes Mellitus, hyperglycemia, hyperthyroidism, hypothyroidism, adrenal insufficiency, or hypophysitis, are eligible if controlled with treatment (≤Grade 1).
14. Have a performance status of 0 or 1 on the ECOG PS.
15. Have adequate organ function as defined in Table 8. Specimens must be collected within 7 days before the start of study intervention.

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16. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load before allocation.

    Note: Participants should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention.

    Hepatitis B screening tests are not required unless:

    a) Known history of HBV infection.
    b) As mandated by local health authority.

17. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.

    Note: Participants must have completed curative antiviral therapy at least 4 weeks before allocation.

    Hepatitis C screening tests are not required unless:

    a. Known history of HCV infection.
    b. As mandated by local health authority.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. For Cohort D and F (DLBCL and NHL): Has lymphoplasmacytic lymphomas, Waldenstrom's macroglobulinemia, chronic lymphocytic leukemia (not associated with small lymphocytic lymphoma), Burkitt (-like) lymphoma, mature T-cell and NK cell neoplasms, immunodeficiency associated lymphoproliferative neoplasms, or histiocytic and dendritic cell neoplasms.
2. For Cohort E (MM):
   a) Has oligo-secretory myeloma, plasma cell leukemia, smoldering multiple myeloma, monoclonal gammopathy of undetermined significance.
   b) History of primary amyloidosis, hyperviscosity or POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).
3. For Cohort F (EBV+ DLBCL): For patients with EBV+ DLBCL should NOT be associated with a solid organ transplant.
4. Has known prior or current CNS involvement.
5. A WOCBP who has a positive urine pregnancy test within 72 hours before study intervention allocation (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

   Note: If 72 hours have elapsed between the screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed and must be negative in order for participant to start receiving study medication.
6. Has clinically significant cardiovascular disease within 12 months from first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability.

   Note: Medically controlled arrhythmia would be permitted.
7. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
8. Has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 3 years.

   Note: The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, squamous-cell carcinoma of the skin, superficial bladder cancer, in situ cervical cancer, or other in situ cancers.

Prior/Concomitant Therapy

9. Has received prior therapy with an mAb blocking TIGIT, an anti-TIGIT agent or an agent modulating the TIGIT axis, or an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent (except where specified) or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

   Note: Participants in Cohort B, relapsed or refractory cHL or PMBCL, must have been previously treated with an anti-PD-1/L1 agent.

   Note: Participants with toxicities to prior anti-PD-1/L1 therapy will be excluded unless their toxicities have resolved to ≤Grade 1 and/or permanent discontinuation is mandated per Table 11. Exceptions include participants with Grade 1-4 hypothyroidism, Grade 2 hyperthyroidism, and Grade 2 hyperglycemia (in combination with evidence of β-cell failure).

10. Any PMBCL participants in Cohort A and B that require the use of urgent cytoreductive therapy.
11. Has received prior systemic anticancer therapy, including investigational agents, within 2 weeks (small molecules like kinase inhibitors) or 4 weeks (chemotherapies and monoclonal antibodies) before cohort allocation.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible. Participants with endocrine-related AEs ≤Grade 2 requiring treatment or hormone replacement may be eligible. For consideration of AEs related to previous treatment with anti-PD-1/L1 therapies, see note below criterion #9 above.

12. If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery before starting study intervention.
13. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must not require ongoing corticosteroid use, and not have >Grade 1 radiation pneumonitis or other radiation-related toxicities. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
14. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines is allowed. Refer to Section 6.5 for information on COVID-19 vaccine.

Prior/Concurrent Clinical Study Experience

15. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks before the first dose of study intervention.

    Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent

Diagnostic Assessments

16. Known severe hypersensitivity to MK-7684A, vibostolimab or pembrolizumab and/or any of its excipients.
17. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority. Refer to Appendix 7 for country-specific testing requirements.
18. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
19. Has an active infection requiring systemic therapy.
20. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
21. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
22. Has present or progressive accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks before enrollment.
23. Has dual active HBV infection (HBsAg (+) and /or detectable HBV DNA) and HCV infection (anti-HCV Ab (+) and detectable HCV RNA) at study entry.

Other Exclusions

24. Participant, in the judgment of the investigator, is unlikely to comply with the study procedures, restrictions, and requirements of the study.
25. Has had an allogenic hematopoietic stem cell/solid organ transplantation within the last 5 years. Participants who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of Graft versus Host Disease

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.3.3 Activity Restrictions

No restrictions are necessary.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Participants who fail screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

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6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies MK-7684A coformulation will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 9

All study interventions will be administered in the clinic setting.

Table 9 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Part 1: Cohorts A to F	Experimental	MK-7684A	Biological/Vaccine	Injection, Solution	Vibostolimab 200mg+ pembrolizumab 20 mg/ 20mL vial	200 mg/ 200 mg	IV Infusion	Q3W up to 35 cycles	Test Product	IMP	Central

EEA=European Economic Area, IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q3W=every 3 weeks.

The classification of IMP and NIMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

MK-7684A = coformulated as 200 mg vibostolimab and 200 mg pembrolizumab

Only participants that achieved SD, PR, or CR after initial treatment or first course followed by an investigator-determined disease progression as per disease-specific criteria will be eligible for a second course of treatment.

All supplies indicated in Table 9 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 8.1.9 for details regarding administration of the study intervention.

6.1.1 Initial Treatment or First Course

The initial treatment or first course of MK-7684A coformulation consists of 35 treatments, administered Q3W. Note: The number of treatments is calculated starting with the first dose.

For participants who have attained a CR (confirmation of CR is required for MM participants) and have been treated for at least 8 cycles (at least 24 weeks) beyond the initial CR date (initial CR confirmation date for MM participants), treatment may be stopped.

6.1.2 Second Course of Study Treatment

All participants who have SD, PR, or CR may be eligible for up to an additional 17 cycles of MK-7684A if there is investigator-determined disease progression as per disease-specific criteria (see Appendix 8) after initial treatment or first course has been completed or stopped for confirmed CR, PR or SD. This retreatment is the second course of this study.

Note: For participants in Cohort E (MM), confirmation of CR is required beyond the initial CR date.

Participants may enter the second course if all of the following criteria are met:

1. No new anticancer treatment was administered after the last dose of study intervention
2. The participant meets all of the inclusion criteria and none of the exclusion criteria
3. The study is ongoing

An objective response or disease progression that occurs during the second course will not be counted as an event for the primary analysis of either endpoint in this study.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of MK-7684A are provided in the Pharmacy Manual.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants enrolled in Part 1 of the study will be assigned to receive study intervention within the appropriate cohort as described in Section 5.1.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.2 for dose modification and toxicity management for irAEs associated with MK-7684A and for other allowed dose interruptions of MK-7684A.

Participants will receive study intervention in the clinic setting directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the treatment period. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on-study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

All treatments that the investigator considers necessary for a participant’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the eCRF including all prescriptions, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

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6.5.2 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Sections 6.6.1, 6.6.2, and 6.6.3. Note: If after the evaluation of the event, it is determined not to be related to MK-7684A, the investigator does not need to follow the treatment guidance. Refer to Table 10 in Section 6.6.2 and Table 11 in Section 6.6.3 for guidelines regarding dose modification and supportive care.

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Dose Modification and Toxicity Management of Hematological AEs Related to MK-7684A

No dose modifications are required for ≤Grade 3 hematological AEs.

In the event of Grade 4 hematological AE that is associated with study treatment (pembrolizumab monotherapy, coformulations, or IO combinations), MK-7684A will not be resumed until the AE has returned to ≤Grade 1.

6.6.2 CCI

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6.6.3 CCI

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Table 11 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤Grade 1 after corticosteroid taper.

irAEs	**Toxicity Grade (CTCAE v5.0)**	**Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations**	**Corticosteroid and/or Other Therapies**	**Monitoring and Follow-up**
Pneumonitis	Grade 2	Withhold	· Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper · Add prophylactic antibiotics for opportunistic infections	· Monitor participants for signs and symptoms of pneumonitis · Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	· Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	· Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) · Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis · Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of b-cell failure	Withhold [a]	· Initiate insulin replacement therapy for participants with T1DM · Administer antihyperglycemic in participants with hyperglycemia	· Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	· Administer corticosteroids and initiate hormonal replacements as clinically indicated	· Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	· Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	· Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue a		
Hypothyroidism	Grade 2, 3 or 4	Continue	· Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	· Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	· Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	· Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	· Based on severity of AE administer corticosteroids	· Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	Withhold	· Based on severity of AE administer corticosteroids	· Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	· Based on severity of AE administer corticosteroids	· Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	· Based on severity of AE administer corticosteroids	· Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event b		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

a The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

b Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

6.6.4 Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab Monotherapy, Coformulations (MK-7684A), or IO Combinations

Pembrolizumab monotherapy, coformulations (MK-7684A), or IO combinations may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab monotherapy, coformulations (MK-7684A), or IO combinations associated infusion reactions are provided in Table 12.

Table 12 Pembrolizumab Monotherapy, Coformulations (MK-7684A), or IO Combinations Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.	Participant may be premedicated 1.5 h (±30 min) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study intervention.	No subsequent dosing

CTCAE=Common Terminology Criteria for Adverse Events; h=hour; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs.
Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov

6.6.5 Other Allowed Dose Interruption for Pembrolizumab Monotherapy, Coformulations (MK-7684A), or IO Combinations

Pembrolizumab monotherapy, coformulations (MK-7684A), or IO combinations may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks of the originally scheduled dose and within 84 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment regimen will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Disease progression outlined in Section 8.2.4 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond disease progression).
- Any occurrence of another malignancy that requires active treatment.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.
- Any prohibited medication listed in Section 6.5.1.

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study is outlined in the Laboratory Manual.

Repeat or unscheduled samples may be taken for safety reasons (where clinically indicated) or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant, or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 CCI

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8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after

the participant provides documented informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

General medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. All other prior malignancies should be recorded, regardless of timeframe.

Details regarding the disease for which the participant has enrolled in this study, ie, hematological malignancy, will be recorded separately and not listed as general medical history.

8.1.5 Baseline Disease Characteristics

The investigator or qualified designee will obtain prior and current details regarding hematological malignancy under the study. Initial primary diagnosis, prior anticancer therapies, and known genetic alterations/mutational status will be recorded. If applicable, prior history of acute and/or chronic GVHD, maximum grade, and dates will be collected.

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8.1.6 Prior and Concomitant Medications Review

8.1.6.1 Prior Medications

The investigator or qualified designee will review before medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before first dose of study intervention/vaccination.

8.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. Refer to Section 6.5.1 for prohibited medication.

8.1.7 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before intervention allocation. Each

participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.8 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.9 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual.

8.1.9.1 Timing of Dose Administration

MK-7684A will be administered using a 30-minute, IV infusion every 3 weeks. The Pharmacy Manual contains specific instructions for MK-7684A reconstitution, preparation of the infusion fluid, and administration. All study treatment will be dosed on Day 1 of each 21-day cycle. For Cycle 1 Day 1, study medication must be administered within 3 days of randomization. After Cycle 1 Day 1, study medication may be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle for administrative reasons.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10.1 CCI [redacted]

CCI [redacted]

CCI

[redacted]

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 CCI [redacted]

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[redacted]

CCI [redacted]

8.2.1 CCI [redacted]

8.2.1.1 CCI [redacted]

CCI [redacted]

CCI [redacted]

8.2.2 CCI [redacted]

8.2.2.1 CCI [redacted]

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8.2.3 CCI [redacted]

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[redacted]

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[redacted]

8.2.4 CCI [redacted]

8.2.4.1 CCI [redacted]

CCI [redacted]

8.2.4.2 CCI [redacted]

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[redacted]

8.2.4.3 CCI [redacted]

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[redacted]

8.2.5 [redacted]

[redacted]

8.2.6 [redacted]

[redacted]

8.3 [redacted]

[redacted]

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

A full physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at screening only. Height will be measured and recorded at screening only and weight will be measured and recorded according to the SoA in Section 1.3.

Other system-based examinations should be included if clinically indicated.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated. New clinically significant abnormal findings should be recorded as AEs.

Other system-based examinations should be included if clinically indicated.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

Vital signs will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiration rate.

8.3.3 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG PS (see Appendix 9) as specified in the SoA (Section 1.3). Screening assessment is required to be performed within 7 days of treatment allocation.

8.3.4 Electrocardiograms

12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in Section 1.3, using an ECG machine that automatically calculates the heart rate and measures pulse rate, QRS, QT, and QTc intervals.

8.3.5 Lymphoma B Symptoms (Cohorts A to D, and F; cHL, PMBCL, FL, DLBCL, and NHL)

These symptoms include the following:

- Unintentional weight loss ≥10% within the previous 6 months.
- Significant fatigue (ie, ECOG PS 2 or worse; cannot work or unable to perform usual activities).
- Fever of 100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
- Night sweats for ≥1 month without evidence of infection.

8.3.6 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 30 days (90 days if considered an SAE) after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

For all cohorts (A to F), thyroid function tests (T3, T4, and TSH) are required at Screening and as per SoA in Section 1.3. Free T3 and free T4 are acceptable.

For Cohorts A to D, and F (cHL, PMBCL, FL, DLBCL, and NHL), LDH and beta-2 microglobulin parameters will be included as per SoA in Section 1.3.

For Cohort E (MM) screening LDH and beta-2 microglobulin levels will be recorded and IgG, IgM, IgA will be monitored. IgD/E is only required for participants with IgD/E myeloma, where serum M-protein cannot be followed otherwise, as per SoA in Section 1.3.

8.3.7 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1. WOCBP require negative serum test within 72 hours or negative urine test within 24 hours before each dose of study intervention. The definition of WOCBP is provided in Appendix 5.1.
  - Pregnancy testing (serum as required by local regulations) should be conducted every cycle (Q3W) during intervention.
  - Pregnancy testing (serum as required by local regulations) should be conducted at the end of relevant systemic exposure (ie, 120 days after the last dose of MK-7684A).
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

8.3.8 CCI

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8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE unless it results in hospitalization or death as described in Section 8.4 and Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

Adverse events will not be collected for participants during the prescreening period (for determination of archival tissue status) as long as that participant has not undergone any protocol-specified procedure or intervention. If the participant requires a blood draw, fresh tumor biopsy, etc, the participant is first required to provide consent to the main study, and AEs will be captured according to guidelines for standard AE reporting.

Refer to Section 4.3.4 for DLT definition.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through 120 days after cessation of study intervention, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 13.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 13 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the

participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

8.4.7 CCI

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8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as ≥3 times the protocol-specified dose for MK-7684A. No specific information is available on the treatment of overdose of MK-7684A. In the event of overdose, study intervention should be discontinued, and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

All reports of MK-7684A overdose with and without an AE must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper.

Reports of either MK-7684A overdose without any associated clinical symptoms or abnormal laboratory results, should be reported using the terminology “accidental or intentional overdose without adverse effect.”

8.6 Pharmacokinetics

To further evaluate MK-7684A immunogenicity and exposure in various hematological malignancies, sample collections for analysis of ADA and PK are currently planned as shown in Section 1.3. Predose blood samples will be obtained to measure PK of serum vibostolimab and pembrolizumab and postdose blood samples will measure PK of serum MK-7684A. Serum C_{max} and C_{trough} at planned visits and times will be summarized.

8.6.1 Blood Collection for Plasma MK-7684A

Sample collection, storage, and shipment instructions for plasma samples will be provided in the Laboratory Manual.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be in Laboratory Manual.

8.8 Biomarkers

CCI

[redacted]

8.8.1 CCI

CCI

[redacted]

8.9 Future Biomedical Research Sample Collection

CCI

[redacted]

8.10 Health Economics Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

After the approval of Amendment 5, the follow up, survival follow up and ongoing assessments per original SoA are amended.

The study will end 90 days after the last participant completes 35 cycles of treatment or terminates early, whichever comes first, and second course option for treatment is no longer available. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study, and no further imaging or participant contacts will be required.

8.11.1 Screening

Approximately 28 days before intervention allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor. Visit requirements are outlined in the SoA (Section 1.3.1).

8.11.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.

For participants eligible for a second course of treatment (see Section 6.1.2), visit requirements are outlined in the SoA (Section 1.3.3).

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study treatment due to disease recurrence or start of a new anticancer therapy will have Safety Follow-up and then proceed directly to Survival Follow up Phase as outlined in the SoA (Section 1.3.4) and in Section 8.11.4.

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed.

8.11.4 Poststudy Visits

After approval of Amendment 5, participants will not be offered second course treatment. This will not affect participants already receiving the second course treatment.

The study will end 90 days after the last participant completes 35 cycles of treatment or terminates early, whichever comes first, and second course option for treatment is no longer available. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study, and no further visits will be required.

8.11.4.1 Safety Follow-up Visit

Safety Follow-up Visits can be at clinic or telephone visit.

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before initiation of a new anticancer treatment, whichever comes first.

Participants who are eligible for a second course of treatment with MK-7684A may have up to 2 Safety Follow-up Visits: 1 after the initial treatment or first course and 1 after the second course.

8.11.4.2 Efficacy Follow-up Visits

Efficacy Follow-up Visits are required for participants who withdraw from treatment without disease progression and have not received new anticancer therapy. Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin Efficacy Follow-up and should be assessed Q12W to monitor disease status for Cohorts A to D, and F (cHL, PMBCL, FL, DLBCL, and NHL), Q4W for Cohort E (MM). Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end-of-study or if the participant begins retreatment with MK-7684A as detailed in Section 6.1.2. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Participants who are eligible to receive retreatment with MK-7684A according to the criteria in Section 6.1.2 will move from Efficacy Follow-up to second course when they experience disease progression. Details are provided in the SoA (Section 1.3.3) for retreatment with MK-7684A.

8.11.4.3 Survival Follow-up Contacts

Survival Follow-up Visits are required for participants that withdraw from treatment for disease progression or have started other anticancer therapy.

Participant Survival Follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first Survival Follow-up assessment should be scheduled as described below:

1. For participants who discontinue treatment intervention and who will not enter Efficacy Follow-up, the first Survival Follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).
2. For participants who completed assessments in Efficacy Follow-up, the first Survival Follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below. The comprehensive plan is provided in Section 9.2 through Section 9.12.

Study Design Overview	A Phase 2, open-label, nonrandomized study to evaluate the safety and efficacy of MK-7684A and vibostolimab monotherapy in participants with various hematological malignancies. The study will be divided into 2 parts: signal finding (Part 1) and cohort expansion (Part 2).
CCI [redacted]	
Primary Endpoints	Part 1: Safety assessed by number of participants with and/or rates of: • Dose-limiting Toxicities • Adverse Events • Discontinuation of study intervention due to an AE
Secondary Endpoints	Part 1: • Objective response rate assessed per disease criteria by investigator • Duration of response as assessed by investigator per relevant disease response criteria (Appendix 8) • Disease control rate as assessed by investigator per relevant disease response criteria (Appendix 8) • Pharmacokinetic endpoints including: C_{trough} and C_{max} Note: CR, PR, and PD in lymphoma participants do not require confirmation. Stringent CR, CR, VGPR, PR, and PD in MM participants require confirmation via 2 consecutive laboratory assessments.
Statistical Methods for Key Efficacy Analyses	Separately for each disease cohort, the point estimate of ORR and DCR will be provided, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934)[Clopper, C. J. and Pearson, E. S. 1934]. Time to event analyses (DOR) will be based on Kaplan-Meier estimation and corresponding 95% CIs.

Statistical Methods for Key Safety Analyses	Counts and percentages of participants with AEs will be provided. The estimate of the DLT rate among participants treated with MK-7684A in the DLT assessment period and the 95% confidence interval for the estimate will be provided.
Interim Analyses	In Part 1, safety data will be examined on a continuous basis during the DLT evaluation window. The first interim safety review will be performed when there are 12 DLT evaluable subjects who have completed at least 2 cycles of treatment. For efficacy data, each cohort will be reviewed individually to assess efficacy signal. Details are provided in Section 9.7.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	Overall, approximately 330 participants may be enrolled into both parts of the study; the planned sample in Part 1 may include approximately 180 participants with relapsed/refractory disease in Cohorts A to F to be administered MK-7684A; the planned sample size in Part 2 may include approximately 120 participants with relapsed/refractory disease in Cohorts B to E to be administered MK-7684A and approximately 30 participants in Cohort G to be administered vibostolimab monotherapy. A target sample size of approximately 390 participants will be used for study planning purposes.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study is being conducted as a nonrandomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

9.3 Hypotheses/Estimation

There are no hypotheses to be tested in this study. Objectives of the study are outlined in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy/Pharmacokinetics Endpoints

After the approval of Amendment 5, the tertiary/exploratory endpoints will not be pursued after the study ends.

Secondary (Part 1)

- **Objective Response Rate**

  The ORR is defined as the percentage of participants who achieve a CR or PR (for MM this includes stringent CR, CR, and VGPR), as assessed by investigator per disease-specific criteria (see Appendix 8).

- **Duration of Response**

  For participants who show an objective response, as assessed by investigator per disease-specific criteria, duration of response is defined as the time from the first documented evidence of an objective response (CR or PR [for MM this includes stringent CR, CR, and VGPR]) until disease progression or death due to any cause, whichever occurs first.

- **Disease Control Rate**

  The DCR is defined as the percentage of participants who have achieved stringent CR, CR, PR (for MM, also including VGPR, MR), or have showed SD for at least 12 weeks before any evidence of progression, per disease-specific criteria (see Appendix 8) as assessed by investigator.

- **Pharmacokinetic endpoints**

  PK endpoints will include vibostolimab C_{trough} and C_{max} parameters.

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9.4.2 Safety Endpoints

The primary endpoint of Part 1 is the number and proportion of participants with DLTs, with AEs, and who discontinue study treatment due to AEs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

A description of safety measures is provided in Section 8.3.

9.4.3 CCI

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9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

Efficacy analyses will be conducted in the APaT population, which consists of all allocated participants who received at least 1 dose of study treatment.

9.5.2 Safety Analysis Population

Safety analyses will be conducted in the APaT population, which consists of all allocated participants who received at least 1 dose of study treatment.

In Part 1, the DLT evaluable population includes the first 12 participants who meet the criteria for DLT evaluability of at least 2 cycles of treatment without discontinuation from study treatment, further detailed in Section 5.5.1. Section 4.3.4 describes the definition of DLTs.

At least 1 laboratory, vital sign, or ECG measurement obtained after at least 1 dose of study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 PK Populations

PK analyses will be conducted in the APaT, which consists of all allocated participants who received at least 1 dose of study treatment, who have a valid C_{trough} and/or C_{max} measurement, within the permissible visit window.

9.5.4 PRO Analysis Population

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[redacted]

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the secondary objectives. The efficacy analyses for ORR, DCR, and DOR will include responses and documented progression events that occur before second course treatment. Methods related to exploratory objectives will be described in the supplemental SAP.

Efficacy analyses will be performed for Part 1 and for combined data of Part 1 and Part 2.

9.6.1.1 Objective Response Rate

The assessment of the ORR by investigator is a secondary endpoint for Part 1. Estimation of the ORR based on disease-specific criteria will be conducted; Lugano 2014 criteria for Cohorts A to D and F (participants with lymphoma), and IWMG 2016 criteria for Cohort E (participants with MM). The point estimate of ORR will be provided per cohort, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934]. Participants with missing data will be considered nonresponders.

9.6.1.2 Duration of Response

The secondary efficacy endpoint of DOR as assessed by investigator will be summarized by cohort. If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who achieve an objective response will be included in this analysis. Censoring rules for DOR are summarized in Table 14; additional details on disease-specific censoring, where needed, will appear in the sSAP. For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responding participants who are alive, have not progressed, have not initiated new anticancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

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9.6.1.3 Disease Control Rate

The assessment of the DCR by investigator is a secondary endpoint. Estimation of the DCR based on disease-specific criteria will be conducted; Lugano 2014 criteria for Cohorts A to D and F (participants with lymphoma), and IWMG 2016 criteria for Cohort E (participants with MM). The point estimate of DCR will be provided per cohort, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934] .

Participants with missing data will be considered nonresponders.

9.6.1.4 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 15.

Table 15 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method (Estimation)	Analysis Population	Missing Data Approach
Primary Analyses			
ORR per disease-specific criteria [a] by investigator	Summary statistics with 95% CI using Exact method based on binomial distribution	APaT	Participants with missing data are considered nonresponders
Key Secondary Analyses			
DOR per disease-specific criteria [a] by investigator	Summary statistics using Kaplan-Meier method	Responders in APaT population	See Table 14 for censoring rules
DCR per disease-specific criteria[a] by investigator	Summary statistics with 95% CI using Exact method based on binomial distribution	APaT	Participants with missing data are considered nonresponders

Abbreviations: APaT=all participants as treated; CI=confidence interval; DCR=disease control rate; DOR=duration of response; ORR=objective response rate.

[a] see Section 8.2.

9.6.2 Statistical Methods for Safety Analyses

Adverse events will be summarized by counts and frequencies for each cohort and/or pooled across cohorts. In addition, the broad AE categories consisting of the percentage of participants with any AE, a drug-related AE, a SAE, an AE, which is both drug-related and serious, and who discontinued due to an AE will be summarized in the same manner. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate. Safety data from second course of treatment will be excluded from the primary analyses.

For Part 1 (signal finding), the estimate of the DLT rate among the first 12 evaluable participants treated in Part 1 and the 95% confidence interval for the estimate will be provided.

9.6.3 CCI

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9.6.4 Baseline Characteristics, Demographics, and Other Analyses

9.6.4.1 Demographic and Baseline Characteristics

Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized. The number and percentage of participants

screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. These analyses will be performed by cohort and overall.

9.6.4.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

Pharmacokinetic parameters will be summarized by planned visit and time.

9.7 CCI

9.7.1 CCI

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[redacted]

9.7.2 Efficacy Interim Reviews

9.7.2.1 Efficacy Futility Review

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

9.9 Sample Size and Power Calculations

Part 1 (signal finding) Sample Size:

Approximately 30 participants may enroll per cohort (Cohorts A to F). With 30 participants in each cohort, the maximum half-width of the two-sided 95% exact confidence interval for ORR within each cohort is 18.7%.

Part 2 (cohort expansion) Sample Size:

Approximately 30 participants may enroll per cohort (Cohorts B to E and G) and this is the target sample size used for study planning purposes.

Since this study does not have formal hypotheses to be tested, no power calculations will be incorporated.

9.10 CCI

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9.11 Compliance (Medication Adherence)

Study intervention is administered at the investigational institution. Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

Extent of Exposure for a participant is defined as the number of cycles in which the participant receives the study medication. Summary statistics will be provided on the Extent of Exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data

protection rights of all participants, trial site staff and, where applicable, third parties. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this

information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names

and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

Not applicable.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- Hematology, chemistry, and urinalysis testing detailed in Table 19 will be performed by the local laboratory.
- Additional individual laboratory assessments, including INR/PT/aPTT, LDH, beta-2 microglobulin, FSH (see Appendix 5), thyroid function, and serum immunoglobulin levels, as well as pregnancy test (see Appendix 5) and infection tests (HCV, HBV and HIV), are described in SoA.
- Biochemical assessment for MM participants as detailed in SoA (Section 1.3) will also be performed by the local laboratory. If investigative sites do not have the capability to perform the required parameters listed in the protocol, samples may be submitted for central laboratory analysis. Investigators should contact the Sponsor to request this.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 19 Hematology, Chemistry, and Urinalysis Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices (optional): MCV MCH Reticulocytes (optional)	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN (urea for sites that do not perform BUN)	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	CrCl OR GFR	Sodium	ALT/SGPT	Total Protein
	Glucose (Investigator should specify if sample is fasting or nonfasting)	Calcium	Alkaline phosphatase	

Laboratory Assessments	Parameters
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, leukocyte (esterase) Bilirubin, urobilinogen, nitrite are optional by UA or dipstick Abnormal urine dipstick will trigger microscopic examination/full urine analysis
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; UA=urinalysis; ULN=upper limit of normal.	

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Any new cancer (that is not a condition of the study). Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**
- **Is life-threatening**
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
  - In offspring of participant taking the product regardless of time to diagnosis.
- **Other important medical events**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study).
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**
  - **Exposure**: Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course**: Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge**: Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)
  - **Rechallenge**: Was the participant re-exposed to the Sponsor's product in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE

MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- **Consistency with study intervention profile**: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] Failure rate of <1% per year when used consistently and correctly.
• Progestogen-only subdermal contraceptive implant[c] • IUS[d] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] Failure rate of <1% per year when used consistently and correctly.
• Combined (estrogen- and progestogen- containing) hormonal contraception[c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). c If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. d IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 CCI [redacted]

10.7.1 CCI [redacted]

CCI [redacted]

10.7.2 CCI [redacted]

CCI [redacted]

10.7.3 CCI [redacted]

CCI [redacted]

10.8 Appendix 8: Response Criteria

10.8.1 Lugano Classification (Cohorts A to D, and F)

Lugano Classification 2014 [Cheson, B. D., et al 2014].

This appendix describes the process for assessing treatment response according to the Lugano Classification [Cheson, B. D., et al 2014] ("Lugano" from now on) for malignant lymphoma. This assessment includes anatomic imaging with CT or MRI (size assessments of lymph nodes, extranodal lesions, spleen, and liver), metabolic imaging (whole body assessment with FDG-PET), and clinical findings (physical examination and bone marrow biopsy results), when these are available and appropriate.

Anatomic imaging may include CT, MRI or some combination of the 2, with details specified in the Site Imaging Manual. CT is the most common modality used, and for the purposes of this document the term "CT" will be used to represent all anatomic imaging, no matter which imaging modality is used.

Before treatment ("baseline"), on CT all focal lesions (nodal and extranodal) will be classified as "target" (selected for quantitative assessment) and "nontarget" (selected for qualitative assessment). The spleen will be assessed quantitatively (by measuring the vertical length), and the liver will be assessed qualitatively. The FDG-PET will be assessed using the 5-point scale (a method similar to the older Deauville criteria [Barrington, S. F., et al 2014]). If bone marrow biopsy is performed, or if there are any physical examination findings that cannot be evaluated by imaging, these should be documented.

After therapy has begun, response assessment will include anatomic response based on CT (when a CT is available), which includes target, nontarget, and new focal lesions, as well as spleen and liver size assessment. Metabolic response, when an FDG-PET is available, will be based on the 5-point scale along with qualitative assessment of changes in FDG uptake from preceding timepoints. Anatomic response, metabolic response, and clinical information will be combined to produce the overall response for each timepoint. The criteria are summarized in the table below, and detailed in the following sections.

Lugano Summary Table

The following tables summarize the assessments based on both CT and PET, as described in the summary table in the original publication [Cheson, B. D., et al 2014]. For details about implementation, please see the sections following the tables. LDi – Longest diameter, SDi – Short axis diameter, PPD – product of perpendicular diameters, SPD – sum of products of diameters.

Complete Response (CR)

CR	PET-Based Response – CMR	CT/MRI-Based Response - CR
Target lesions	Score 1, 2, or 3	Target nodes/nodal masses regress to <1.5 cm in LDi; no extranodal sites of disease remain
Nontarget lesions	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, negative by immunohistochemistry

CMR = complete metabolic response; CR = complete response; CT = computed tomography; FDG = 2-fluorodeoxyglucose; LDi = longest diameter; MRI = magnetic resonance imaging; PET = positron emission tomography.

Partial Response (PR)

PR	PET-Based Response – PMR	CT/MRI-Based Response - PR
Target lesions	Score 4 or 5 without new lesions Reduced overall uptake (extent and/or intensity) compared with baseline	≥50% decrease from baseline in SPD of target lymph nodes and extranodal sites (up to 6)
Nontarget lesions	Not applicable	Anything other than progression
Organ enlargement	Not applicable	Spleen must have regressed by ≥50% in excess length
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline. If there are persistent focal changes in the marrow in the context of a nodal response and without recent growth factor use, perform biopsy, or consider MRI, or an interval scan.	Not applicable

CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography; PMR = partial metabolic response; PR = partial response; SPD = sum of products of diameters.

Stable Disease (SD)

SD	PET- Based Response – SMD	CT/MRI-Based Response - SD
Target lesions	Score 4 or 5 (without new lesions) No significant change in FDG uptake from baseline or nadir	<50% decrease from baseline in SPD of target lesions. No lesion shows progression
Nontarget lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

CT = computed tomography; FDG = 2-fluorodeoxyglucose; MRI = magnetic resonance imaging; PET = positron emission tomography; SD = stable disease; SMD = stable metabolic disease; SPD = sum of products of diameters.

Progressive Disease (PD)

PD	PET-Based Response – PMD	CT/MRI-Based Response - PD
Target lesions	Score 4 or 5 with an increase in overall uptake (extent and/or intensity) from baseline	Growth of any target lesion: Increase ≥50% from nadir PPD and Increase in LDi or SDi from nadir of: ≥0.5 cm for lesions <2 cm ≥1.0 cm for lesions ≥2 cm and Current LDi >1.5 cm for a lymph node or ≥1.0 cm for an extranodal lesion
Nontarget lesions	Not applicable	Clear progression of preexisting nontarget lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another cause (eg, infection, inflammation). If uncertain regarding cause of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in LDi A new extranodal site of any size, as long as its presence is unequivocal and attributable to lymphoma
Organ enlargement		When splenomegaly was already present, the excess length must increase by >50% (≥1 cm absolute increase) from nadir. If no prior splenomegaly, or prior splenomegaly had resolved, spleen length must increase by ≥2 cm to >13 cm.

PD	PET-Based Response – PMD	CT/MRI-Based Response - PD
Bone marrow	New or recurrent FDG-avid foci, confirmed by biopsy	New or recurrent involvement

CT = computed tomography; FDG = 2-fluorodeoxyglucose; LDi = longest diameter; MRI = magnetic resonance imaging; PET = positron emission tomography; PD = progressive disease; PMD = progressive metabolic disease; PPD = product of perpendicular diameters; SDi = short axis diameter.

Anatomic Disease Assessment

Anatomic assessment specifically refers to the size of focal lesions or organs, assessed using computed tomography or magnetic resonance imaging. As stated previously, for simplicity the term "CT" will be used to represent all anatomic imaging.

Screening (Baseline) Assessment

Documentation of focal lesions

All focal lesions caused by lymphoma are identified at baseline and classified as measurable or nonmeasurable. Up to 6 of the measurable lesions are selected to serve as "target" lesions, which are then followed quantitatively throughout the study. All other focal lesions are documented as "nontarget" lesions, and evaluated qualitatively thereafter.

Measurable and nonmeasurable lesions

Malignant lymph nodes (nodal lesions) are considered measurable if they are consistent with lymphoma, clearly and reproducibly measurable in 2 dimensions on an axial slice, and measure >1.5 cm in LDi when assessed by CT/MRI scan, irrespective of scanner type and slice thickness/interval. Extranodal lesions are considered measurable if they are consistent with lymphoma, clearly and reproducibly measurable in 2 dimensions on an axial slice, and are ≥1.0 cm in both LDi and SDi when assessed by CT/MRI scan, regardless of slice thickness. In lymphomas that are FDG-avid, a lesion must be PET-positive (show FDG uptake greater than the surrounding tissue) to be measurable.

Lesions considered nonmeasurable include:

- Lymph nodes and nodal masses that are PET-positive and considered consistent with lymphoma, but that do not meet the size and reproducibility requirements to be considered measurable, and lesions visible on PET but not CT
- PET-negative lesions which meet the size criteria for measurability, and are considered consistent with lymphoma, in lymphoma that shows FDG avidity in other lesions
- Uni-dimensionally measurable lesions (clearly measurable in only one dimension)
- Extranodal lesions which do not meet the requirements for measurability, but are considered to be clearly due to lymphoma

- Truly nonmeasurable/assessable sites of disease, including:
  - Effusions and ascites
  - Bone lesions
  - Brain lesions, CNS lesions, leptomeningeal disease
  - Mucosal lesions in the gastrointestinal tract
  - Pleural, peritoneal or bowel wall thickening

Target and Nontarget Lesions

Up to up to 6 target lesions will be selected from among the measurable lesions and documented as target nodal and target extranodal lesions. Target lesions should be selected based on their size (largest lesions preferred) and suitability for reproducible measurements. Measurements of the LDi and SDi should be made in the axial plane on the slice of the tumor with the longest in-plane diameter. Calculate the PPD for each target lesion and the SPD for all target lesions.

Nontarget lesions will be all focal (nodal and extranodal) lesions that are consistent with lymphoma, but not chosen as target lesions, whether they were measurable or not.

Once lesions are designated as target or nontarget, those designations may not change during later assessments.

Spleen Assessment at Baseline

Splenic involvement will be assessed quantitatively, as a separate category from the assessment of measurable or nonmeasurable focal lesions. The spleen length will be measured from cranial to caudal. All spleen measurements referred to hereafter will refer to this cranio-caudal measurement. The spleen is considered normal if it is less than 13 cm, or if the spleen has been removed surgically. It is considered enlarged if it is greater than 13 cm in length. The portion of the measurement that exceeds 13 cm will be considered the abnormal portion.

Liver Assessment at Baseline

Hepatic involvement will be assessed qualitatively, separately from the assessment of measurable or nonmeasurable disease. At baseline, the liver will be assessed qualitatively as either normal or enlarged, and should only be documented as enlarged if there is clear evidence (based on biopsy or imaging) that the enlargement is due to lymphoma, and not to benign causes.

Anatomic Response (CT-based postbaseline assessment)

Target lesions

At every timepoint after screening, each target lesion is measured. Calculate the PPD for each target lesion and the SPD for all target lesions together. Response categories are as defined below:

- Complete Response: All target lymph nodes must have regressed to normal size defined as ≤1.5 cm in LDi. Target extranodal sites must be absent (0 by 0 cm).
- Partial Response: ≥50% decrease in SPD of target lesions from baseline, and no individual lesion meets the criteria for progression.
- Progressive Disease: Target lesion progression is based on the progression of any single lesion (not a change in the SPD), which meets all of the following requirements:
  - The lesion must have increased by ≥50% from its nadir in PPD.
  - For a lymph node, it must be >1.5 cm in LDi, and for an extranodal lesion it must be ≥1.0 cm in LDi.
  - And one of the following:
    - For lesions <2 cm at nadir, the lesion's LDi or SDi must have increased by ≥0.5 cm at the current timepoint from its nadir.
    - For lesions ≥2 cm at nadir, the lesion's LDi or SDi must have increased by ≥1 cm at the current timepoint from its nadir.
- Stable Disease: A target lesion assessment of SD requires all of the following:
  - Target lesions do not meet the criteria for CR or PR
  - No individual lesion meets the criteria for progression
- Not Evaluable: When a target lesion identified at baseline cannot be evaluated at a postbaseline timepoint due to missing imaging, poor image quality, changes in the lesion or background that precludes assessment, or focal therapy or other procedures that change the lesion size, the target lesion assessment will be NE, unless progression is assessed in another target lesion.

Nontarget lesions

Nontarget lesions will be assessed at each post baseline timepoint individually and as a group. Response categories are as defined below:

- Absent/Normalized (CR): All individual nontarget nodal lesions must have returned to normal size. All extranodal lesions must have disappeared.
- Unequivocal Progression (PD): Any individual nontarget lesion must unequivocally progress in the context of the overall disease burden to be assessed as PD. For increased thickening of the wall of a hollow viscus, the reviewer will use their cautious judgment to determine whether the increase is most likely caused by disease progression.

- PD should not be called based on enlarging pleural effusions or ascites, or enlarging lytic bone lesions, and rather, the overall assessment should be based on the rest of the disease burden.
- Stable Disease: At least one nontarget lesion is still present, or a node enlarged, without any individual lesions showing unequivocal progression.
- Not Evaluable: When an individual nontarget lesion lymph node, extranodal lesion, or nonmeasurable disease cannot be assessed at a postbaseline timepoint due to missing imaging, poor image quality, changes in the lesion or background that precludes assessment, or focal therapy to a lesion, the individual nontarget lesion will be assessed as NE. The assessment of the nontarget lesions as a whole will be NE if any of the nontarget lesions are NE and none are PD.

New lesions

Lesions will be considered new if they were not present at the baseline timepoint but are visible at the current timepoint.

A node consistent with lymphoma will be recorded as a new lesion if it was previously normal in size and is now >1.5 cm in LDi. An unequivocal, new extranodal lesion consistent with lymphoma of any size is considered a new lesion. If multiple new extranodal lesions are noted, at least one should be recorded as a new lesion.

New lesions must be consistent with lymphoma rather than another etiology (eg, infection, inflammation) and must be PET-positive, if PET is available. New lesions will be treated as PET-positive when PET is not available to confirm avidity.

Some types of truly nonmeasurable lesions generally require further verification that they are attributable to lymphoma through biopsy or cytology. These include ascites, pleural or pericardial effusions, and lytic bone lesions. They may be recorded as new lesions only when there is other evidence of progression.

Other truly nonmeasurable lesions will not require verification to be considered a new lesion, as long as their appearance is unequivocal in the judgment of the reviewer:

- Nonmeasurable lesions such as brain and CNS lesions including leptomeningeal disease attributable to lymphoma
- Nonmeasurable nodal masses such as infiltrative mesenteric masses or retroperitoneal masses

Extranodal lesions which disappeared and then reappeared at a later timepoint will have the same effect as a new lesion, but are not designated “new”.

Spleen response

The spleen will be measured in the craniocaudal length as at baseline, and the enlarged portion calculated by subtracting 13 cm. Response categories for the spleen are as defined below:

- Normal (CR): Spleen was enlarged at baseline and has regressed to ≤13 cm at the current timepoint or the spleen was assessed as normal at baseline and is still normal, or there is radiological evidence of splenectomy at baseline.
- Partial Response (PR): Spleen was assessed as enlarged at baseline, and its excess length has decreased by ≥50%.
- Stable Splenomegaly (SD): No decrease consistent with PR and no increase consistent with progression.
- Unequivocal increase (PD): The spleen is assessed as PD if any of the following are true:
  - Recurrent splenomegaly: A spleen which was abnormal at baseline (>13 cm) first returned to normal, but at the current timepoint the spleen increases by >2 cm from its nadir and the length is >13 cm.
  - New splenomegaly: No prior splenomegaly and spleen increases by >2 cm from baseline and the length is >13 cm.
  - Progression of existing splenomegaly: A spleen which is abnormal at baseline has the enlarged portion increase by >50%, and by ≥1 cm in absolute measurement, at the current timepoint from its nadir value.

Liver response

The liver will be assessed qualitatively. Response categories are as defined below:

- Normal (CR): Liver was assessed as enlarged at baseline and has regressed to a normal size or still enlarged but without evidence of lymphoma involvement, OR the liver was assessed as normal at baseline and continues to be normal.
- Stable Disease (SD): Liver is considered stable if there is persistent liver involvement with evidence based on imaging (CT or MRI) or biopsy that there is infiltration by lymphoma of the entire organ.
- Unequivocal increase (PD): New hepatomegaly, recurrent hepatomegaly, or definite growth from prior liver size, and there is evidence that this is due to lymphoma infiltration.

Anatomic Response

The anatomic response should be assessed at each postbaseline timepoint based on the criteria below. Liver size alone should never be the basis for response determination by itself, but only support the assessment as supplemental information.

Target	Nontarget	Spleen	New Lesions	Anatomic Response
CR	CR	CR	No	CR*
CR	CR	PR	No	PR**
CR	SD	CR	No	PR**
PR	CR/SD	CR/PR	No	PR
PR	CR/SD	SD	No	SD
SD	CR/SD	CR/PR	No	SD
SD	CR/SD	CR/PR/SD	No	SD
Any non-PD	NE	CR/PR/SD	No	NE
NE	Any non-PD	CR/PR/SD	No	NE
PD	Any	Any	Any	PD
Any	PD	Any	Any	PD
Any	Any	PD	Any	PD
Any	Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.
*if the liver shows lymphoma involvement, it must resolve to allow CR
**Spleen can drive PR on its own if no target lesions were identified at baseline

Metabolic Response

In addition to anatomic imaging, metabolic imaging using FDG-PET can contribute to the assessment, if it is available, or may form the sole basis for response if no anatomic imaging is performed at a time point. An FDG-PET is required at screening. Subsequent time points that require PET are shown in the schedule of assessments. If lesions are not FDG-avid at baseline, PET is not required at follow-up timepoints unless clinically indicated.

PET Assessment

For every FDG-PET scan, a 5-point scale score is obtained by comparing the SUVmax of the lesion that shows the greatest tracer uptake (the “hottest” lesion) to surrounding normal tissue, to a region of interest (ROI) placed over blood in the heart or major vessels of the mediastinum (the “mediastinal blood pool”) and to an ROI placed over normal liver.

Depending on the uptake, a score between 1-5 will be assigned as follows:

Score	Definition
1	No uptake above background
2	Uptake above background, but below mediastinal blood pool
3	Uptake > mediastinal blood pool, but ≤ uptake in liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver (SUVmax >2 × normal liver) OR (after treatment has started) New FDG-positive lymphoma lesions
FDG = fluorodeoxyglucose; SUVmax = maximum standardized uptake value.	

After screening, in addition to the 5-point scale score the assessment of the FDG-PET also involves an assessment of the overall uptake (a combination of extent and intensity) by tissue consistent with lymphoma, and comparison of this uptake to the baseline and to the scan on which the overall uptake was lowest (nadir).

Metabolic response determination

Metabolic response categories are defined as follows:

Metabolic Response	Definition
Complete metabolic response (CMR)	A score of 1, 2, or 3
Partial metabolic response (PMR)	A score of 4 or 5 (without new lesions), AND Overall uptake decreased compared with baseline
Stable metabolic disease (SMD)	A score of 4 or 5 (without new lesions), AND Overall uptake unchanged compared with baseline and nadir
Progressive metabolic disease (PMD)	A score of 4 or 5 with overall uptake increased compared with nadir, OR with new FDG-positive lesions consistent with lymphoma

In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue, even if the tissue has high physiologic uptake.

Clinical Data

Bone marrow assessment

To allow an overall response of CR, the bone marrow must be clear of lymphoma (negative for lymphoma).

Lugano allows assessment of bone marrow based on FDG-PET, if the lymphoma type is FDG-avid. Bone marrow on FDG-PET may be normal, may show diffuse uptake (clinical judgment is required because this is also compatible with reactive changes due to chemotherapy or colony-stimulating factors), or may show focal increased uptake that is strongly indicative of lymphoma.

A negative PET allows the bone marrow to be declared negative, even without biopsy, and would support a CR overall (diffuse uptake compatible with reactive changes from chemotherapy or growth factor use can fall into this category). A PR may occur with residual uptake higher than uptake in normal marrow but reduced compared with baseline. If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.

Bone marrow aspirate or biopsy is required only as clinically indicated, or if FDG-PET evaluation of bone marrow is judged inconclusive. For lymphoma that is shown at baseline to be non-FDG-avid, aspiration or biopsy is required to declare marrow to be negative. If bone marrow biopsy is performed and shows lymphoma, the bone marrow is considered positive, regardless of the results of the PET.

Physical examination findings

On rare occasions, lesions may be present on physical examination that are not seen on imaging at all. An example might be lymphadenopathy in the popliteal fossa, when the "whole body" imaging includes only anatomy to the midfemur. Such lesions should be documented as nontarget lesions in study forms. They can contribute to progression if new lesions appear this way, and if any were present at baseline, they must disappear for an overall response of CR.

Other clinical data

Information on the use of hematopoietic growth factors and other medications can affect the response assessment as described above.

At certain protocol-specified time points, additional tissue biopsies may be collected and incorporated into the response assessment.

Overall Response

Overall response at each timepoint is determined by combining the anatomic response, metabolic response, and clinical data.

When both CT and FDG-PET are available, the overall response is driven primarily by the metabolic response. When only one imaging modality is available at a given timepoint, that modality is the main determinant of overall response.

Metabolic Response	Anatomic Response	Bone Marrow	Physical Examination	Overall Response
CMR	CR, PR, or SD	Negative	No lesions	CR
PMR	CR, PR, or SD	Any	No new lesions	PR
SMD	CR, PR, or SD	Any	No new lesions	SD
PMD	Any	Any	Any	PD
Any	PD	Any	Any	PD

CMR = complete metabolic response; CR = complete response; PD = progressive disease; PMD = progressive metabolic disease; PMR = partial metabolic response; PR = partial response; SD = stable disease; SMD = stable metabolic disease.

During determination of overall response, if no FDG-PET was performed at the timepoint in question, the results of a preceding PET may be "carried forward", unless there has been worsening of disease on the CT. For example, if a postbaseline assessment shows a CMR on the PET, and PR on the CT, the overall response is CR. If the next timepoint shows continued PR on the CT, but there is no PET available, the overall response for that visit is still CR.

If there is PR based on either anatomic or metabolic imaging, but a biopsy demonstrates that the tissue in question is not malignant, the response can be upgraded to a CR.

10.8.2 IMWG Consensus Criteria for Response and MRD in MM (Cohort E)

IMWG response criteria 2016 [Kumar, S., et al 2016].

Response assessments for Cohort E will be performed according to the IMWG criteria. The response assessment will include imaging assessments (including plasmacytoma and skeletal assessments), bone marrow results, MRD assessment, serum and urine protein results, serum FLC, and laboratory results.

Overall Response Category Definitions

IMWG MRD criteria (requires a CR as defined below):

- Sustained MRD-negative: MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years).
- Flow MRD-negative: Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.

- Sequencing MRD-negative: Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
- Imaging plus MRD-negative: MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue.

Standard IMWG response criteria

- Stringent CR: CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells).
- Complete response: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates.
- Very good PR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h.
- Partial response:
  - ≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h.
  - If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria;
  - If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.
- Minimal response: ≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.
- Stable disease: Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for CR, VGPR, PR, minimal response, or PD.
- Progressive disease: Any one or more of the following criteria:
  - Increase of 25% from lowest confirmed response value in one or more of the following criteria:
    - Serum M-protein (absolute increase must be ≥0·5 g/dL);

  - Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h);
  - In participants without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL);
  - In participants without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be ≥10%);
- Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis;
- ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease.

10.9 Appendix 9: Eastern Cooperative Oncology Group Performance Status

Grade	Performance Status
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to perform work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Adapted from [ECOG ACRIN Cancer Research Group 2016]

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADR	adverse drug reaction
AE	adverse event
AEOSI	adverse event of special interest
ALK+	anaplastic lymphoma kinase-positive
ALT	alanine aminotransferase
APaT	All Participants as Treated
AST	aspartate aminotransferase
AUC	area under the curve
BM	bone marrow
CAR	Chimeric antigen receptor
CD	cluster of differentiation
cHL	classical Hodgkin's Lymphoma
CI	confidence interval
CL	clearance
Cmax	maximum plasma concentration
CMR	complete metabolic response
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C_{trough}	lowest plasma concentration
DCR	Disease control rate
DLBCL	Diffuse Large B-cell lymphoma

Abbreviation	Expanded Term
DLT	dose-limiting toxicity
DLTe	dose-limiting toxicity evaluable
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein Barr virus
EC	Ethics Committee
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
ECOG PS	Eastern Cooperative Oncology Group Performance Score
EDC	electronic data collection
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EORTC	European Organization for the Research and Treatment of Cancer
ePROs	electronic patient-reported outcomes
EQ-5D-5L	EuroQoL 5D-5L
EuroQoL	European quality of life
FBR	future biomedical research
FcγR	Fc-gamma receptor
FDAAA	Food and Drug Administration Amendments Act
FDG	fluorodeoxyglucose
FISH	fluorescent in situ hybridization
FL	Follicular Lymphoma
FLC	free light chain
FLIPI	Follicular Lymphoma International Prognostic Index
FOXP3	forkhead box P3 protein
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GVHD	graft versus host disease
HBsAg	hepatitis B surface antigen

Abbreviation	Expanded Term
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hodgkin's Lymphoma
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICR	independent central review
ID	identification
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
Ig	immunoglobulin
IgG4	immunoglobulin G4
IHC	immunohistochemistry
IMiD	immunomodulatory drugs
IMP	investigational medicinal product
IMWG	International Myeloma Working Group
IND	Investigational New Drug
IO	immuno-Oncology
IPI	International Prognostic Index
irAEs	immune-related AEs
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
LAG	lymphocyte activation gene

Abbreviation	Expanded Term
LAM	lactational amenorrhea method
LDi	longest diameter
mAb	monoclonal antibody
MCL	Mantle Cell Lymphoma
MIPI	Mantle Cell Lymphoma International Prognostic Index
MIPI-c	MIPI + Ki-67 index
MM	Multiple Myeloma
mPD-1	murine programmed cell death 1 protein
MR	Minor response
MRD	minimal residual disease
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTIGIT	murine TIGIT
MYC	myelocytomatosis
MZL	marginal zone lymphoma
n	number
NCI	National Cancer Institute
NGF	next generation flow
NGS	next generation sequencing
NHL	Non-Hodgkin’s Lymphoma
NK	natural killer cell
NKT	natural killer T-cell
NOS	not otherwise specified
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBMC	peripheral blood mononuclear cells

Abbreviation	Expanded Term
PBPK	Physiologically based PK
PD	progressive disease
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	Progression-free survival
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic
PMBCL	Primary mediastinal B-cell lymphoma
PO	by mouth
PPD	product of perpendicular diameters
PR	partial response
PRN	as needed
PRO	patient-reported outcome
PVRL-2	poliovirus receptor-related 2
Q2W	every 2 weeks
Q3W	every 3 weeks
Q12W	every 12 weeks
Q24W	every 24 weeks
QLQ	quality of life questionnaire
QoL	quality of life
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCT	stem cell transplant
SD	stable disease
SDi	short axis diameter
SLL	Small Lymphocytic Lymphoma

Abbreviation	Expanded Term
SNP	single-nucleotide polymorphism
SoA	schedule of activities
SPD	sum of the product of diameters
SPEP	serum protein electrophoresis
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
SUV	standardized uptake value
SUVmax	maximum standardized uptake value
T3	Triiodothyronine
T4	Thyroxine
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TILs	Tumor-infiltrating lymphocytes
TIM-3	T-cell immunoglobulin and mucin-domain containing-3
TNF	Tumor necrosis factor
TPS	Tumor proportion score
T-reg	Regulatory T-cell
TSH	Thyroid-stimulating hormone
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
VAS	Visual Analog Scale
Vc	central volume of distribution
VGPR	very good partial response
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

11 REFERENCES

[Ansell, S. M., et al 2019]	Ansell SM, Minnema MC, Johnson P, Timmerman JM, Armand P, Shipp MA, et al. Nivolumab for relapsed/refractory diffuse large B-cell Lymphoma in patients ineligible for or having failed autologous transplantation: a single-arm, phase II study. J Clin Oncol. 2019;37(6):481-9.	[05Q7W5]
[Avet-Loiseau, H., et al 2013]	Avet-Loiseau H, Hulin C, Campion L, Rodon P, Marit G, Attal M, et al. Chromosomal abnormalities are major prognostic factors in elderly patients with multiple myeloma: the intergroupe francophone du myelome experience. J Clin Oncol. 2013 Aug 1;31(22):2806-9.	[05QZFN]
[Bai,S., et al 2012]	Bai S, Jorga K, Xin Y, Jin D, Zheng Y, Damico-Beyer LA, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51(2):119-35.	[03T78B]
[Barrington, S. F., et al 2014]	Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Mueller SP, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas imaging working group. J Clin Oncol. 2014 Sep 20;32(27):3048-58. Erratum in: J Clin Oncol. 2016 Jul 20;34(21):2562.	[05QDSG]
[Bjordal, K., et al 2000]	Bjordal K, de Graeff A, Fayers PM, Hammerlid E, van Pottelsberghe C, Curran D, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. Eur J Cancer. 2000 Sep;36(14):1796-807.	[040VGM]

[Carlsten, M., et al 2007]	Carlsten M, Bjorkstrom NK, Norell H, Bryceson Y, van Hall T, Baumann BC, et al. DNAX accessory molecule-1 mediated recognition of freshly isolated ovarian carcinoma by resting natural killer cells. Cancer Res. 2007 Feb 1;67(3):1317-25.	[04GS8V]
[Chauvin, J. M., et al 2015]	Chauvin JM, Pagliano O, Fourcade J, Sun Z, Wang H, Sander C, et al. TIGIT and PD-1 impair tumor antigen-specific CD8$^+$ T cells in melanoma patients. J Clin Invest. 2015 May;125(5):2046-58.	[04GS9H]
[Chauvin, J. M., et al 2015a]	Chauvin JM, Pagliano O, Fourcade J, Sun Z, Wang H, Sander C, et al. TIGIT and PD-1 impair tumor antigen-specific CD8(+) T cells in melanoma patients. J Clin Invest. 2015 May;125(5):2046-58.	[05JHL4]
[Cheson, B. D., et al 2014]	Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-67.	[045PKM]
[Clopper, C. J. and Pearson, E. S. 1934]	Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.	[03Y75Y]
[Dardalhon, V., et al 2005]	Dardalhon V, Schubart AS, Reddy J, Meyers JH, Monney L, Sabatos CA, et al. CD226 is specifically expressed on the surface of Th1 cells and regulates their expansion and effector functions. J Immunol. 2005 Aug 1;175(3):1558-65.	[04GS9P]
[Ding, W., et al 2017]	Ding W, Laplant B, Witzig TE, Johnston PB, Colgan JP, Rech KL, et al. PD-1 blockade with pembrolizumab in relapsed low grade non-Hodgkin lymphoma [abstract]. Blood. 2017;130:4055.	[053P2Q]

[Dirks, N. L. and Meibohm, B 2010]	Dirks NL, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet 2010;49(10):633-59.	[058SQX]
[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]
[Dostalek,M., et al 2012]	Dostalek M, Gardner I, Gurbaxani BM, Rose RH, Chetty M. Pharmacokinetics, pharmacodynamics and physiologically-based pharmacokinetic modelling of monoclonal antibodies. Clin Pharmacokinet 2013;52:83-124.	[03T7LF]
[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[ECOG ACRIN Cancer Research Group 2016]	ECOG-ACRIN Cancer Research Group. ECOG Performance Status [Internet]. Philadelphia: ECOG-ACRIN Cancer Research Group; 2016. Available from: http://ecog-acrin.org/resources/ecog performance-status.	[04JT28]
[Eichenauer, D. A., et al 2014]	Eichenauer DA, Engert A, Andre M, Federico M, Illidge T, Hutchings M, et al. ESMO Guidelines Working Group. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014 Sep;25 Suppl 3:iii70-5.	[048V6B]
[Federico, M., et al 2009]	Federico M, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, Vitolo U, et al. Follicular Lymphoma International Prognostic Index 2: A new prognostic index for follicular lymphoma developed by the International Follicular Lymphoma Prognostic Factor Project. J Clin Oncol 2009;27(27):4555-62.	[03RCM8]

[Freeman, C. L., et al 2019]	Freeman CL, Kridel R, Moccia AA, Savage KJ, Villa DR, Scott DW, et al. Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma. Blood. 2019 Aug 29;134(9):761-4.	[05Q7W8]
[Golan, T., et al 2018]	Golan T, Bauer TM, Jimeno A, Perets R, Niu J, Lee JJ, et al. Phase 1 dose-finding study of the anti-TIGIT antibody MK-7684 as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors. Slides presented at: Society for Immunotherapy of Cancer (SITC) 33rd Annual Meeting; 2018 Nov 7-11; Washington, DC.	[05HVFC]
[Gopal, A. K., et al 2018]	Gopal AK, Schuster SJ, Fowler NH, Trotman J, Hess G, Hou JZ, et al. Ibrutinib as treatment for patients with relapsed/refractory follicular lymphoma: results from the open-label, multicenter, phase II DAWN study. J Clin Oncol. 2018 Aug 10;36(23):2405-12.	[05HPHH]
[Guillerey, C., et al 2018]	Guillerey C, Harjunpaa H, Carrie N, Kassem S, Teo T, Miles K, et al. TIGIT immune checkpoint blockade restores CD8(+) T-cell immunity against multiple myeloma. Blood. 2018 Oct 18;132(16):1689-94.	[05Q7WC]
[Hendrikx, J. J. M. A., et al 2017]	Hendrikx JJMA, Haanen JBAG, Voest EE, Schellens JHM, Huitema ADR, Beijnen JH. Fixed dosing of monoclonal antibodies in oncology. Oncologist. 2017;22:1212-21.	[05JHQC]
[Herrera, A. F., et al 2017]	Herrera AF, Mei M, Low L, Kim HT, Griffin GK, Song JY, et al. Relapsed or refractory double-expressor and double-hit lymphomas have inferior progression-free survival after autologous stem-cell transplantation. J Clin Oncol. 2017 Jan 1;35(1):24-31.	[05Q7WP]

[Hirota, T., et al 2005]	Hirota T, Irie K, Okamoto R, Ikeda W, Takai Y. Transcriptional activation of the mouse Necl-5/Tage4/PVR/CD155 gene by fibroblast growth factor or oncogenic Ras through the Raf-MEK-ERK-AP-1 pathway. Oncogene. 2005 Mar 24;24(13):2229-35.	[04GTZL]
[Horn, H., et al 2013]	Horn H, Ziepert M, Becher C, Barth TFE, Bernd HW, Feller AC, et al. MYC status in concert with BCL2 and BCL6 expression predicts outcome in diffuse large B-cell lymphoma. Blood. 2013 Mar 21;121(12):2253-63.	[05QZFP]
[Hoster, E., et al 2008]	Hoster E, Dreyling M, Klapper W, Gisselbrecht C, van Hoof A, Kluin-Nelemans HC, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008 Jan 15;111(2):558-65. Erratum in: Blood. 2008 Jun 15;111(12):5761.	[05PTTB]
[Hoster, E., et al 2016]	Hoster E, Rosenwald A, Berger F, Bernd HW, Hartmann S, Loddenkemper C, et al. Prognostic value of Ki-67 index, cytology, and growth pattern in mantle-cell lymphoma: results from randomized trials of the european mantle cell lymphoma network. J Clin Oncol. 2016 Apr 20;34(12):1386-94.	[05R2PD]
[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]
[IB Edition 8 2020]	MK-7684/MK-7684A Investigator's Brochure, Edition Number 8, 18-Nov-2020.	[05L37R]
[International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993]	International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993 Sep 30;329(14):987-94.	[05R2PG]

[Johnston, R. J., et al 2014]	Johnston RJ, Comps-Agrar L, Hackney J, Yu X, Huseni M, Yang Y, et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. Cancer Cell. 2014 Dec 8;26(6):923-37.	[04GS9T]
[Josefsson, S. E., et al 2018]	Josefsson SE, Huse K, Kolstad A, Beiske K, Pende D, Steen CB, et al. T cells expressing checkpoint receptor TIGIT are enriched in follicular lymphoma tumors and characterized by reversible suppression of T-cell receptor signaling. Clin Cancer Res. 2018 Feb 15;24(4):870-81.	[05Q8TY]
[Josefsson, S. E., et al 2019]	Josefsson SE, Beiske K, Blaker YN, Forsund MS, Holte H, Ostenstad B, et al. TIGIT and PD-1 mark intratumoral T cells with reduced effector function in B-cell non-Hodgkin lymphoma. Cancer Immunol Res. 2019 Mar;7(3):355-62.	[05Q8V6]
[Keizer,R.J., et al 2010]	Keizer RJ, Huitema ADR, Schellens JHM, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet 2010;49(8):493-507.	[03T7M7]
[King, M. T. 1996]	King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. Quality of Life Research 1996;5:555-67.	[03Q4R5]
[Kumar, S., et al 2016]	Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016 Aug;17(8):e328-46.	[04LPJ8]
[Landgren, O. 2007]	Landgren O, Caporaso NE. New aspects in descriptive, etiologic, and molecular epidemiology of Hodgkin's lymphoma. Hematol Oncol Clin North Am. 2007 Oct;21(5):825-40.	[04HXLR]

[Lesokhin, A. M., et al 2016]	Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. J Clin Oncol. 2016 Aug 10;34(23):2698-704.	[0537CC]
[Levin, S. D., et al 2011]	Levin SD, Taft DW, Brandt CS, Bucher C, Howard ED, Chadwick EM, et al. Vstm3 is a member of the CD28 family and an important modulator of T-cell function. Eur J Immunol. 2011 Apr;41(4):902-15.	[04GT88]
[Li, W., et al 2018]	Li W, Blessin NC, Simon R, Kluth M, Fischer K, Hube-Magg C, et al. Expression of the immune checkpoint receptor TIGIT in Hodgkin's lymphoma. BMC Cancer. 2018;18:1209.	[05Q7WS]
[Lozano, E., et al 2020]	Lozano E, Mena MP, Diaz T, Martin-Antonio B, Leon S, Rodriguez-Lobato LG, et al. Nectin-2 expression on malignant plasma cells is associated with better response to TIGIT blockade in multiple myeloma. Clin Cancer Res. 2020 Sep 1;26(17):4688-98.	[05Q7WY]
[Mahindra, A., et al 2012]	Mahindra A, Laubach J, Raje N, Munshi N, Richardson PG, Anderson K. Latest advances and current challenges in the treatment of multiple myeloma. Nat Rev Clin Oncol. 2012 Feb 21;9(3):135-43.	[0460D3]
[Mateos, M. V., et al 2019]	Mateos MV, Blacklock H, Schjesvold F, Oriol A, Simpson D, George A, et al. Pembrolizumab plus pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma (KEYNOTE-183): a randomised, open-label, phase 3 trial. Lancet Haematol. In press 2019.	[0597DC]

[Minnie, S. A., et al 2018]	Minnie SA, Kuns RD, Gartlan KH, Zhang P, Wilkinson AN, Samson L, et al. Myeloma escape after stem cell transplantation is a consequence of T-cell exhaustion and is prevented by TIGIT blockade. Blood. 2018 Oct 18;132(16):1675-88. Erratum in: Blood. 2019 Nov 21;134(21):1878.	[05QZFR]
[Moskowitz, C. H., et al 2018]	Moskowitz CH, Walewski J, Nademanee A, Masszi T, Agura E, Holowiecki J, et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. Blood. 2018 Dec 20;132(25):2639-42.	[05R2PF]
[National Comprehensive Cancer Network, Inc. 2008]	National Comprehensive Cancer Network I. NCCN Clinical practice guidelines in oncology: Non-Hodgkin's lymphomas (Version 3.2008). http://www.nccn.org. (accessed 10-Mar-2008)	[03QNLK]
[Niu, J., et al 2020]	Niu J, Nagrial A, Voskoboynik M, Chung HC, Lee DH, Ahn MJ, et al. Safety and efficacy of vibostolimab, an anti-TIGIT antibody, plus pembrolizumab in patients with anti-PD-1/PD-L1-naive NSCLC [abstract]. Presented at: European Society for Medical Oncology (ESMO) Virtual Congress; 2020 Sep 19-21/Oct 16-18; [online meeting]. Ann Oncol. 2020;31(suppl 4):S891-2. Abstract no. 1410P.	[05PWYN]
[Osoba, D., et al 1998]	Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16(1):139-44.	[03RL72]
[Palumbo, A., et al 2014]	Palumbo A, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, Morgan G, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. J Clin Oncol. 2014 Feb20;32(6):587-600.	[045NNH]

[Palumbo, A., et al 2015]	Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol. 2015 Sep 10;33(26):2863-9. Supplemental appendix; 8 p.	[05QZFV]
[Rajkumar, S. V., et al 2014]	Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014 Nov;15(12):e538-48.	[0469BV]
[Ribrag, V., et al 2019]	Ribrag V, Avigan DE, Green DJ, Wise-Draper T, Posada JG, Vij R, et al. Phase 1b trial of pembrolizumab monotherapy for relapsed/refractory multiple myeloma: KEYNOTE-013 [correspondence]. Br J Haematol. 2019;186:e41-4.	[05MZ4T]
[Rosenwald, A., et al 2003]	Rosenwald A, Wright G, Leroy K, Yu X, Gaulard P, Gascoyne RD, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med. 2003 Sep 15;198(6):851-62.	[045PY3]
[Savage, K. J., et al 2003]	Savage KJ, Monti S, Kutok JL, Cattoretti G, Neuberg D, De Leval L, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. Blood. 2003 Dec 1;102(12):3871-9.	[045R66]
[Solal-Céligny, P., et al 2004]	Solal-Céligny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, et al. Follicular lymphoma international prognostic index. Blood 2004;104(5):1258-65.	[03RLYL]

[Sonneveld, P., et al 2016]	Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, Anderson KC, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016 Jun 16;127(24):2955-62.	[05QZFY]
[Soriani, A., et al 2009]	Soriani A, Zingoni A, Cerboni C, Iannitto ML, Ricciardi MR, Di Gialleonardo V, et al. ATM-ATR-dependent up-regulation of DNAM-1 and NKG2D ligands on multiple myeloma cells by therapeutic agents results in enhanced NK-cell susceptibility and is associated with a senescent phenotype. Blood. 2009 Apr 9;113(15):3503-11.	[04GT8W]
[Stanietsky, N., et al 2009]	Stanietsky N, Simic H, Arapovic J, Toporik A, Levy O, Novik A, et al. The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. Proc Natl Acad Sci U S A. 2009 Oct 20;106(42):17858-63.	[04GTYX]
[Steidl, C. 2011]	Steidl C, Gascoyne RD. The molecular pathogenesis of primary mediastinal large B-cell lymphoma. Blood. 2011 Sep 8;118(10):2659-69.	[04Q08J]
[Sunseri, N., et al 2019]	Sunseri N, Chen X, Wald N, Preillon J, Smith SM, Driessens G, et al. Beyond PD-1: investgation therapeutic potential of TIGIT blockade in DLBCL [abstract]. Blood. 2019 Nov 13;134(suppl 1):391.	[05R8HX]
[Swerdlow, S. H., et al 2016]	Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016 May 19;127(20):2375-90.	[04KTLT]
[U.S. Prescribing Information 2020]	U.S. Prescribing Information: KEYTRUDA (pembrolizumab) injection, for intravenous use: Nov 2020.	[05Q5QF]

[Usmani, S. Z., et al 2019]	Usmani SZ, Schjesvold F, Oriol A, Karlin L, Cavo M, Rifkin RM, et al. Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naive multiple myeloma (KEYNOTE-185): a randomised, open-label, phase 3 trial. Lancet Haematol. In press 2019.	[0597DD]